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EXPERIMENTAL STUDIES ON HEADACHE

A. CONTRAST OF HISTAMINE HEADACHE WITH THE HEADACHE OF MIGRAINE AND THAT ASSOCIATED WITH HYPERTENSION

B. CONTRAST OF VASCULAR MECHANISMS IN PREHEADACHE AND IN HEADACHE PHENOMENA OF MIGRAINE

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There is evidence that stretched cranial arteries give rise to certain headaches.[1] Evidence has also been presented to show that the cerebral arteries, principally the large arteries at the base of the brain, are responsible for the quality and intensity of the headache which follows intravenous injection of histamine and that the extracerebral arteries make only a minor contribution to the histamine headache.[2] The headaches of migraine and hypertension, on the other hand, result largely from the stretch and dilatation of arteries in the scalp and dura.[3] Experiments briefly alluded to in previous communications, but not reported in detail (the effect of increased intracranial pressure on histamine headache), form in part the basis for these inferences. These experiments are presented fully in the present report.

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1. (*a*) Pickering, G. W., and Hess, W.: Observations on the Mechanism of Headache Produced by Histamine, Clin. Sc. **1**:77, 1933. (*b*) Clark, D.; Hough, H., and Wolff, H. G.: Experimental Studies on Headache: Observations on Histamine Headache, Arch. Neurol. & Psychiat. **28**:140 (July) 1932. (*c*) Graham, J. R., and Wolff, H. G.: Mechanism of Migraine Headache and Action of Ergotamine Tartrate, ibid. **39**:737 (April) 1938.

2. (*a*) Schumacher, G. A.; Ray, B. S., and Wolff, H. G.: Experimental Studies on Headache: Further Analysis of Histamine Headache and Its Pain Pathways, Arch. Neurol. & Psychiat. **44**:701 (Oct.) 1940. (*b*) Ray, B. S., and Wolff, H. G.: Experimental Studies on Headache: Pain-Sensitive Structures of the Head and Their Significance in Headache, Arch. Surg. **41**:813 (Oct.) 1940.

3. Sutherland, A. M., and Wolff, H. G.: Experimental Studies on Headache: Further Analysis of the Mechanism of Headache in Migraine, Hypertension and Fever, Arch. Neurol. & Psychiat. **44**:929 (Nov.) 1940.

The experiments herein described have as their aim, first, the further analysis of the vascular mechanisms underlying migraine headache and headache associated with arterial hypertension, and, second, an analysis of the mechanisms of the preheadache phenomena of migraine. As a basis for the concepts to be developed, additional experiments clarifying the mechanism of histamine headache were first carried out.

In an earlier communication from this clinic regarding the mechanism of migraine headache [1c] it was pointed out that there were as yet insufficient data to permit conclusions concerning the state of the cerebral arteries during the attack. Though it was postulated that this type of headache arose largely from the extracerebral vessels, the recurrence of headache following injection of histamine after it was abolished by ergotamine tartrate left the relation of migraine headache to histamine headache unsettled. The following data indicate clearly the contrasting mechanisms of these two types of headache.

I. EFFECT OF INCREASING THE INTRACRANIAL PRESSURE

The first group of experiments is based on the assumption that certain of the cranial arteries, by virtue of their location, can be supported extramurally by increasing the cerebrospinal fluid pressure, thereby diminishing their amplitude of pulsation and thus reducing headache.

The large cerebral arteries at the base of the brain, notably those forming the circle of Willis and its branches, are obviously susceptible of extramural compression, with increase in cerebrospinal fluid pressure. Extracranial (scalp) arteries, of course, are outside the direct influence of changes in intracranial pressure. The effect on dural arteries will be considered subsequently.

A method has therefore been devised to increase cerebrospinal fluid pressure rapidly by connecting the subarachnoid space with a high column of fluid (sterile physiologic solution of sodium chloride) in order to observe the effect of such increase in pressure on the intensity of the headache. As has been stated, the experiments rest on the premise that reduction in headache by this means is due to increased support of stretched cranial arteries. In headache due to dilatation of cranial arteries reduction in pain would indicate that intracranial arteries are responsible, whereas no change in intensity would bespeak an extracranial origin.

Method.—Subjects in whom headache was induced by injection of histamine and subjects with spontaneous headache associated with migraine, hypertension or hypertension with renal failure were studied. After spinal puncture, with the patient in the horizontal position, the cerebrospinal fluid pressure was increased by connecting with the lumbar subarachnoid space a flask of sterile fluid elevated 800 to 1,000 mm. above the spinal canal. The extent to which the intracranial pressure was increased was regulated by the height of the column of fluid above the spinal canal.

(*a*) *Histamine Headache.*—As a background for the experiments concerned with migraine and headache associated with hypertension, a previously described observation on histamine headache was confirmed, namely, that a rise in the cerebrospinal fluid pressure lessens the headache. In 13 patients in whom spinal puncture was necessary for diagnosis, the effect of increasing intracranial pressure on headache induced by histamine was investigated.

Severe headache was induced within sixty seconds by the intravenous administration of 0.10 to 0.15 mg. of histamine phosphate. Such a headache reached its maximum intensity quickly, remaining there for five to eight minutes in most instances, after which it gradually subsided and was gone within ten to twelve minutes.

Method: In the experiments on subjects with histamine headache, the level of the column of fluid was elevated 800 to 1,000 mm. above the spinal canal. A clamp was removed from the connecting tube when it was desired to increase the cerebrospinal fluid pressure rapidly and was replaced when further increase in pressure was no longer desired. To reduce pressure rapidly the clamped tube was disconnected and the fluid allowed to flow freely from the subarachnoid space. Pressure readings by means of the usual glass water manometer were taken at intervals.

Shortly after the onset of headache, and approximately at the time when it reached its maximum intensity, the pressure was suddenly raised as described to 800 or 1,000 mm. of physiologic solution of sodium chloride. If headache subsequently was abolished the fluid was then allowed to flow from the subarachnoid space until the pressure was greatly reduced. If headache recurred the pressure was again raised until the headache was eliminated. This sequence of events was repeated as often as the duration of a given histamine headache permitted.

Results: Of the 13 subjects, there were 2 from whom adequate information could not be obtained, owing to apprehension or difficulty in understanding. In 11 the headache was eliminated or grew less when the intracranial pressure was increased. In 7 of the latter there was a constant relationship between increase in cerebrospinal fluid pressure and abolition of the headache. In these subjects there was always a recurrence of severe headache following rapid reduction in pressure. In the other 4 patients, because of distracting paresthesias or insufficient severity of the headache, the relation of increase in pressure to decrease in intensity of headache was not clearly defined, but in 3 of the 4 subjects headache recurred when the pressure was diminished.

In 7 attacks of headache induced by histamine the pain was abolished fourteen times, each time by increasing the cerebrospinal fluid pressure, and was brought back after each abolition by an immediately ensuing reduction in the pressure. In 2 of the 7 cases headache was abolished once and recurred once on decreasing pressure. In 3 it was abolished and allowed to recur twice. In 2 attacks of headache, pain was

abolished and reinduced by this procedure three times (fig. 1). Furthermore, in none of these 7 attacks of headache was there an instance in which increase in pressure failed to eliminate the pain.

The average initial, or "resting," pressure, measured before the headache was induced, was 145 mm. of solution of sodium chloride. The average manometric pressure at which headache was eliminated was 480 mm. of solution of sodium chloride (with a range of 350 to 550 mm.). The average pressure on return of headache was 190 mm. (with a range of 185 to 240 mm.). Cerebrospinal fluid pressure after each increase in pressure was rapidly reduced until the headache

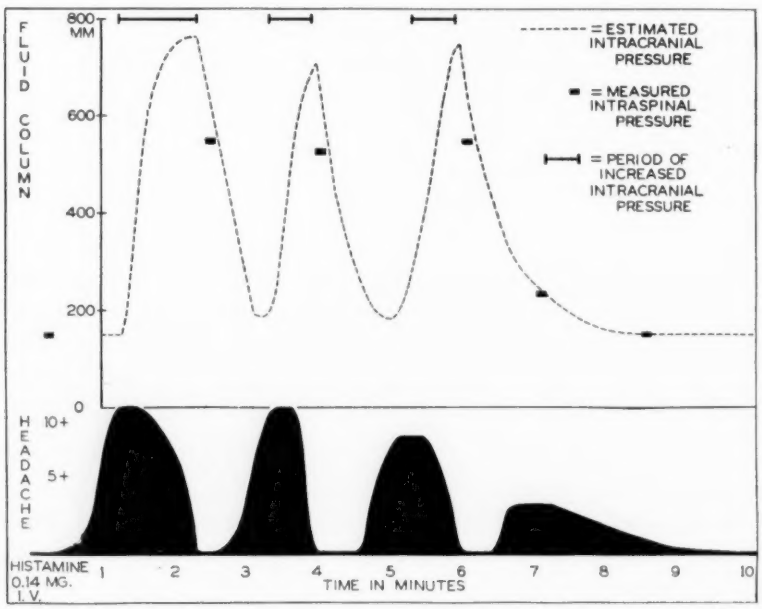

Fig. 1.—Abolishing effect of repeated experimental increases in the intracranial pressure on a headache induced by the intravenous injection of 0.14 mg. of histamine phosphate.

returned to its former severity. The average amount of fluid removed to reach this state was 12 cc. (with a range of 8 to 15 cc.).

The average time from the moment of increasing the cerebrospinal fluid pressure to the first definite awareness of reduction in the headache was thirty-five seconds (with a range of fifteen to ninety seconds). The average time from the moment of increase in pressure to elimination of the headache was seventy seconds (with a range of twenty-five to one hundred and twenty seconds). The average length of time required for headache to recur (from the moment that pressure began to fall) was forty-five seconds (with a range of fifteen to ninety seconds).

(*b*) *Migraine Headache.*—In 7 subjects spinal puncture was performed during an attack of migraine headache.

Method: In the subjects with headache associated with migraine, hypertension and hypertension with renal failure the method was identical. The cerebrospinal fluid pressure was varied by progressively increasing the height of the fluid column above the spinal canal. Usually it was elevated from 0 (at the level of the spinal canal) to from 750 to 1,000 mm. above, in stages, several minutes between each successive increase being allowed for adjustments in pressure to occur. To reduce pressure, the level of the solution of sodium chloride was dropped to that of the spinal canal, and at the termination of the experiment fluid was allowed to flow freely from the subarachnoid space.

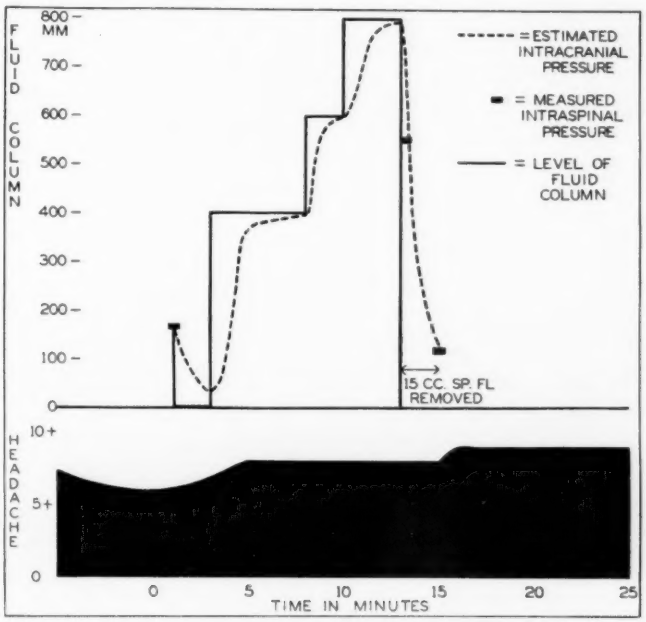

Fig. 2.—Failure of induced increase in the intracranial pressure to diminish the intensity of an attack of migraine headache.

Results: In 6 of the subjects no change in the intensity of the migraine headache occurred after increasing subarachnoid pressures to the level of 700 to 1,000 mm. of solution of sodium chloride for fifteen to thirty minutes (fig. 2). In 1 of these 6 subjects (fig. 3), a woman aged 33, with recurrent attacks of severe hemicrania for twenty years, hypertension of a mild degree (165 systolic and 100 diastolic to 180 systolic and 120 diastolic) had developed within the preceding six months. The results in the seventh subject are discussed later.

(*c*) *Headache Associated with Hypertension.*—This phrase is used to designate recurrent headache in persons with hypertension but without renal failure and hypertensive encephalopathy.

Results: Two subjects with unbearable headaches associated with hypertension (200 systolic and 130 diastolic and 235 systolic and 150 diastolic, respectively) but without renal failure (azotemia) or papilledema and with normal initial spinal fluid pressure were investigated. In 1 subject there was no relationship between change in the cerebrospinal fluid pressure and the intensity of the headache (fig. 4). Though the headache diminished somewhat in intensity during the course of the experiment, there was no correlation between this change and the induced changes in pressure. This subject was a man of 49 whose headaches were associated with high blood pressure, averaging 170 to

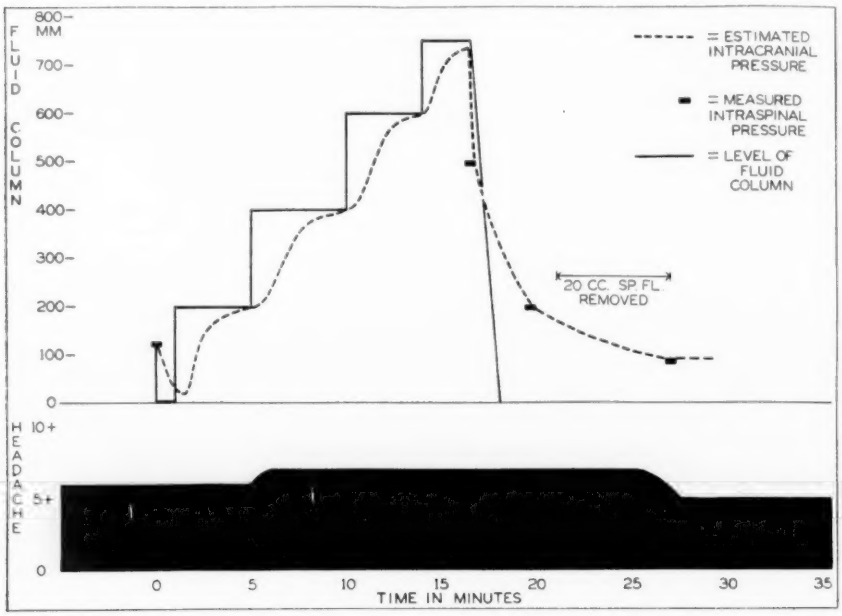

Fig. 3.—Lack of effect of artificially increasing intracranial pressure on the intensity of a headache in a subject with long-standing migraine in whom hypertension had recently developed.

200 systolic and 130 diastolic for several years. However, he had had recurrent severe headaches since the age of 7. The second subject is discussed later.

Comment.—Two subjects, one in the migraine and the other in the hypertension group, noted reduction in the intensity of the headache during increase in the cerebrospinal fluid pressure. In 1 of these, however (the subject in the hypertension group), dramatic disappearance of the headache occurred under identical experimental conditions except that, unknown to the patient, the cerebrospinal fluid pressure was not

elevated. The results in both instances were considered to be due to psychologic changes induced by the instrumentation, especially since it was observed during this work that migraine headaches and those associated with hypertension would occasionally undergo spontaneous reduction while preparations were being made to carry out an experiment.

The contrast between the headache of migraine and that associated with hypertension, on the one hand, and histamine headache, on the other, in their response to increase in the intracranial pressure adds

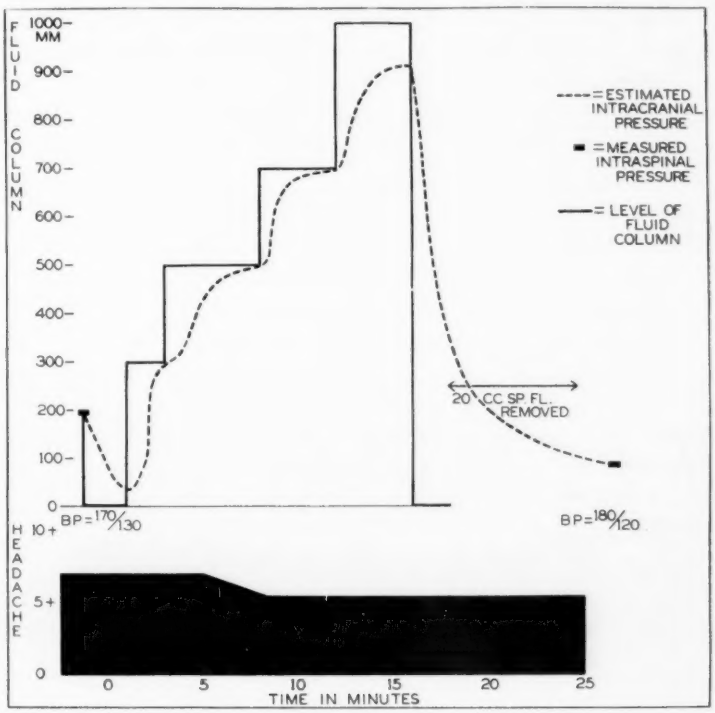

Fig. 4.—Failure of increase in the intracranial pressure to reduce materially the intensity of headache in a subject with hypertension.

further evidence that the site of dilated and stretched arteries giving rise to headache is the same for the headache of migraine and that of hypertension, but different for the headache produced by histamine. The fact that histamine headache is reduced by increasing intracranial pressure favors the contention that dilatation and stretch of the cerebral arteries, notably the larger branches of the circle of Willis, at the base of the brain, are responsible for histamine headache, since it is likely that these vessels are supported by increasing the cerebrospinal fluid pressure. That reduction in histamine headache following increase in

cerebrospinal fluid pressure is not due, even in part, to increased support of the dural arteries is probable, since it has been shown [2a] that histamine headache is just as intense in the absence of these vessels.

It has been previously observed that the extracranial arteries participate in the vasodilatation induced by histamine and may therefore be a factor in histamine headache. However, it was also suggested that their contribution to the headache is so slight as compared with that from the cerebral vessels as to be negligible. This inference is borne out by these experiments, since in 7 of the 11 subjects the headache was eliminated by raising the intracranial pressure. In the remaining 4 subjects a minor contribution to the headache may have been made by the extracerebral arteries.

After injection of histamine the average increase in amplitude of pulsation of the intracranial arteries was 350 per cent in 13 subjects, the increase being as much as 730 per cent in 1 of these. In contrast, the average increase in amplitude of pulsation of the temporal artery in 27 subjects experiencing histamine headache was 138 per cent. In short, after injection of histamine the intracranial arteries undergo greater increase in amplitude of pulsation than the extracranial arteries.

Although increase in amplitude of pulsations of extracranial arteries may produce headache, such increase after injection of histamine in most instances does not account for the histamine headache. Indeed, as already shown, histamine headache, with its increase in amplitude of pulsation of both intracranial and extracranial arteries,[4] is usually abolished when the amplitude of pulsation of the intracranial arteries alone is diminished.

This apparent contradiction raises no serious problem. A plausible explanation for the absence of pain from arteries of the scalp in histamine headache is found in the relaxed state of the arterial walls in the scalp and the decreased peripheral resistance, due to dilatation of the minute vessels which follow injection of histamine. This in essence creates a different physiologic system from that which occurs in the absence of histamine. The more nearly vessels approach the condition represented by rigid tubes the smaller the expansion produced by equal increments of pressure (*a* and *b*), or, inversely, the farther vessels deviate from such a rigid system the greater the expansion produced by equal increments of pressure. The latter state approaches that following injection of histamine. Because of a lowered local intravascular pressure, cardiac systole may cause an augmented amplitude of pulsation of arteries in the scalp without raising the pressure beyond that which exists normally. An increase in amplitude of about 100 per cent under these circumstances would not entail painful distention. When the increase in

4. Clark, Hough and Wolff,[1b] Schumacher, Ray and Wolff.[2a]

amplitude approaches 400 per cent or more, as it does with the cerebral arteries, the pressure exceeds that which exists normally, and thus painful impulses arise.

In short, the adequate pain stimulus is an increase in intravascular pressure sufficient to cause deformity of pain end organs in or about arterial walls. The deformity of the end organs and the intravascular pressure are therefore closely related, but equal increments of amplitude of pulsation do not represent equal deformity of end organs. Because of the relaxed state of the arteries and the lowered intravascular pressure after injection of histamine, the deformity of the walls of the arteries in the scalp is not usually sufficient to stimulate pain end organs, and consequently headache seldom arises from this source.

With migraine headache the situation is otherwise. Here the arteries of the scalp, though relaxed, are much less so than after injection of histamine.[3] Moreover, in migraine headache there is no evidence of peripheral vasodilatation of small vessels, as after histamine. Therefore, an amplitude of pulsation in the scalp arteries of about 100 per cent above normal would represent considerable increment in pressure and cause deformity of pain end organs, with resultant headache.

A headache sometimes mistaken for migraine and allied to the histamine headache insofar as it involves the cerebral arteries is the headache associated with intracranial aneurysms, which are usually found on the circle of Willis and its branches. The initial fierce headache can be explained by distention or rupture of these pain-sensitive arteries.

As mentioned, there is evidence [3] which indicates that the headache associated with hypertension and migraine has its origin in dilatation of the arteries of the scalp and dura. That increase in the cerebrospinal fluid pressure does not relieve such headache supports this conception. Extracranial arteries cannot be compressed by increase in the intracranial pressure, and it is likely that the dural arteries, by virtue of their protected position, are much less supported by the increased pressure than are the large subarachnoid (cerebral) arteries at the base.

In his monograph on hypertension, published in 1913,[5] Janeway called attention to the not infrequent occurrence of migraine headache during early life in persons who later had hypertension and "hypertensive headaches." It has been pointed out elsewhere that the headaches of migraine and those associated with hypertension are often indistinguishable.[3] In addition, individual attacks of migraine headache and the headache associated with hypertension both respond dramatically to vasoconstrictor drugs, notably ergotamine tartrate.[3]

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5. Janeway, T. C.: A Clinical Study of Hypertensive Cardiovascular Disease, Arch. Int. Med. **12**:755 (Dec.) 1913.

(*d*) *Headache Associated with Renal Failure and Hypertension (Hypertensive Encephalopathy).*—To be distinguished from the headache associated with hypertension is the headache associated with renal failure, hypertension and azotemia. The latter occasionally occurs as a terminal manifestation in persons who for many years have had headache in association with hypertension without renal failure. As can be seen from the following experiment, the mechanisms in these headaches are not identical.

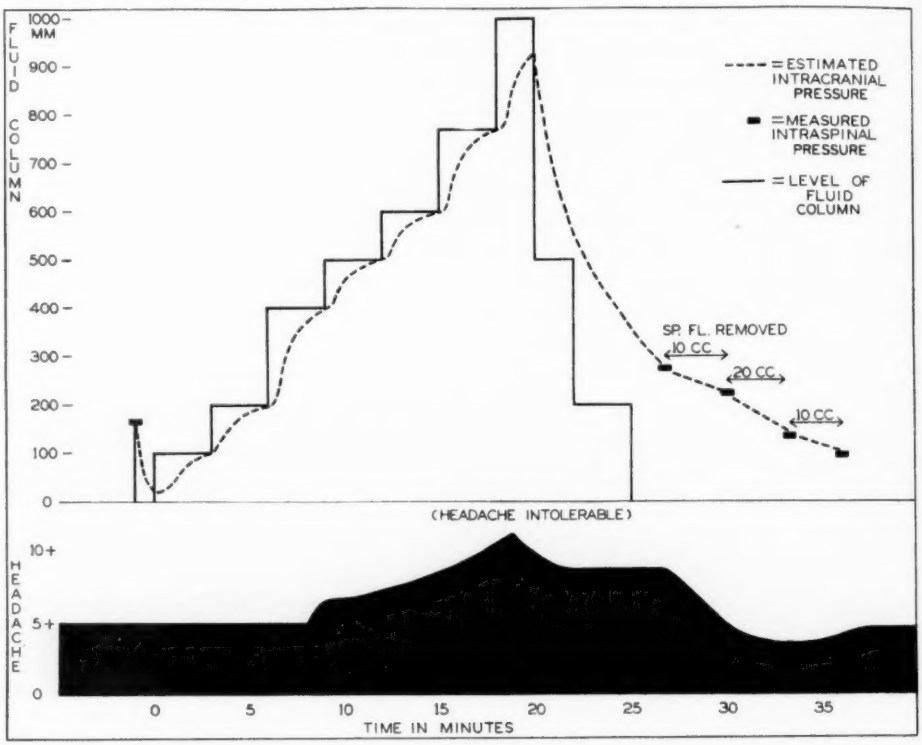

Fig. 5.—Aggravation of headache on increasing the intracranial pressure in a subject with hypertensive encephalopathy and renal failure. It is to be noted that the initial cerebrospinal fluid pressure was normal and that even with the final reduction in pressure to below its original level the headache was not ameliorated as compared with its original intensity.

Experiment.—The patient, aged 29, was gravely ill with chronic glomerulonephritis (marked hypertension, azotemia, edema of the extremities, retinal hemorrhages, exudates, vomiting and severe headaches, but no papilledema). During a moderately severe headache the cerebrospinal fluid pressure was experimentally increased (sterile solution of sodium chloride). The subject's headache became unbearably intense when the fluid column was gradually elevated to 1,000 mm. and improved when the pressure was reduced (fig. 5).

At the beginning of the experiment the patient's headache was about half its maximum potential severity, i. e., about 5 plus, 10 plus being considered as maximum in the patient's experience. The initial, or "resting" pressure of the spinal fluid was 170 mm. of solution of sodium chloride. When the fluid column had reached a height of 1,000 mm. above the canal, after progressive elevation over a period of twenty minutes, the subject complained bitterly of intolerable headache. Gradual reduction of the pressure by lowering the fluid column to 0 resulted in concomitant amelioration of headache to 7 plus, i. e., an intensity which, according to the subject, was still greater than the original. At this time the measured manometric spinal fluid pressure was 280 mm. Removal of 10 cc. of fluid resulted in further improvement of the headache to 5 plus and a reduction of manometric pressure to 230 mm. Removal of another 20 cc. of fluid caused additional slight amelioration of the pain to 4 plus and a decrease in pressure to 140 mm. A final 10 cc. was removed, causing the pressure to drop to 100 mm., but at this time the headache was thought to be slightly worse, 5 plus.

Comment: It is to be noted that unlike the histamine headache, which is abolished by raising the cerebrospinal fluid pressure, and unlike the migraine headache or that associated with hypertension alone, which is unchanged by increasing the intracranial pressure, the headache in this patient was actually made worse by this procedure. What are the implications of this fact? If the headache were the result of relaxation and distention of the cerebral arteries, then increasing the cerebrospinal fluid pressure would reduce its intensity. If the headache were the result of relaxation and distention of the extracerebral arteries alone, increasing the cerebrospinal fluid pressure would not influence the intensity of the headache. Hence, since the headache in this patient with hypertension and renal failure was made worse, some other mechanism must be invoked, though distention of extracerebral arteries may have played a part.

It has been pointed out that there are at least six mechanisms involved in production of headache.[2b] These include, besides the mechanism involved in migraine and histamine headache, i. e., distention of the extracranial and intracranial arteries, the following: traction on the pain-sensitive veins tributary to the great sinuses; traction on the pain-sensitive arteries at the base of the brain; traction on the meningeal arteries; inflammation of the pain-sensitive dura on the floor of the anterior and posterior fossae, and direct pressure on nerves containing afferent fibers for pain, such as the fifth, ninth and tenth cranial and the upper three cervical nerves. It is to be noted that there is to date no convincing evidence that increased intracranial pressure per se induces headache.[2b]

A reasonable explanation of the headache associated with hypertensive encephalopathy is that local edema of the brain[6] results in

6. Rosenberg, E. F.: The Brain in Malignant Hypertension: A Clinicopathologic Study, Arch. Int. Med. **65**:545 (March) 1940.

traction on or displacement of the tributary veins to the great venous sinuses. Increase in traction could follow increase in pressure and thus cause increase in headache. But decrease in pressure by withdrawing spinal fluid would not necessarily decrease the local edematous state causing the initial traction and headache. The fact that headache was unchanged by spinal fluid drainage in this patient with hypertensive encephalopathy may be analogous to the failure of spinal fluid drainage to reduce the headache in some patients with tumors of the brain (with or without increased intracranial pressure).[7]

An investigation of spinal fluid pressure in arterial hypertension by Shelburne and his associates[8] is relevant. Though headache was found to be more frequent when the intracranial pressure was increased and when accompanied by papilledema, it occurred in the absence of either. Lumbar drainage did not usually decrease headache. In at least 14 of 16 instances of headache with arterial hypertension and increased intracranial pressure, the headache was not decreased by lowering the spinal fluid pressure by spinal drainage.

In short, it seems likely that the headache of hypertensive encephalopathy involves entirely different mechanisms from those under consideration in migraine and in the headache associated with hypertension without encephalopathy. Such mechanisms will be considered further in subsequent studies on headache resulting from displacement of and traction on pain-sensitive vascular structures. Mention of this type of headache is made now so that the mechanisms of these two varieties of "hypertensive" headaches may not be confused.

CEREBRAL ARTERIES AND PREHEADACHE MIGRAINE PHENOMENA

Little accurate information is at hand concerning the mechanism of the preheadache phenomena of migraine. To be sure, these so-called preheadache phenomena are not always followed by headache; indeed, in some subjects they are never followed by headache. In about half of the subjects having migraine headaches such preheadache symptoms occur. They are commonly visual, such as scotomas, hemianopia, scintillations and other crude hallucinations of light and color. Less common are paresthesias or defects of motility, often unilateral.

Of these, scotomas are the most readily investigated, and an opportunity for their study was afforded by their occurrence in Dr. A. M. Cahan, who made accurate and rapid observations of his own visual

7. Northfield, D. W. C.: Some Observations on Headache, Brain **61**:133, 1938.

8. Shelburne, S. A.; Blain, D., and O'Hare, J. D.: Spinal Fluid in Hypertension, J. Clin. Investigation **11**:489, 1932.

defects. The preheadache scotomas in this subject were predictable in their span and of long enough duration that experimental modifications in intensity were followed by a return of the visual defect to its original state. Several observations were made during a single attack.

To ascertain whether dysfunction of the cerebral vasculature is responsible for this preheadache symptom, a vasodilator agent, amyl nitrite, known to affect cerebral vessels, was employed. It is justifiable to infer that cerebral vasodilatation induced without a fall in blood pressure increases cerebral blood flow, whereas a sharp drop in blood pressure, regardless of the state of the cerebral arteries, decreases the

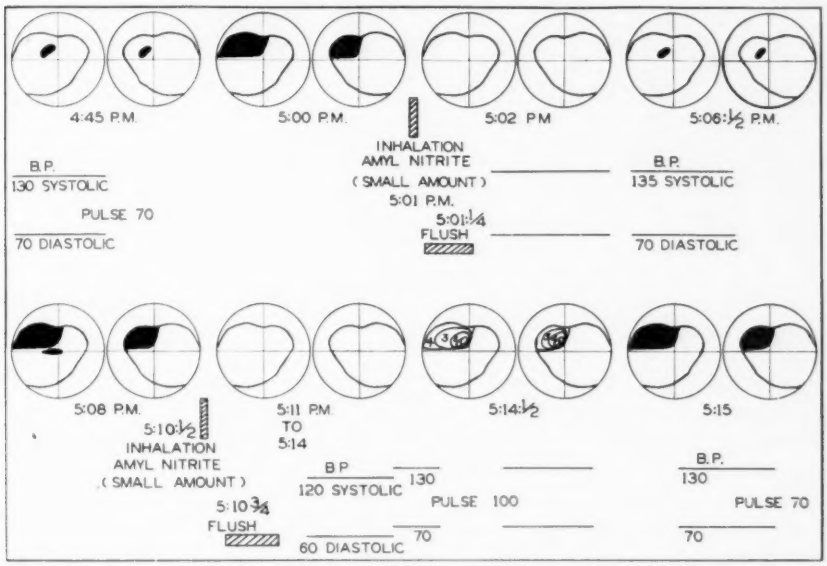

Fig. 6.—Effect of inhaling a small amount of amyl nitrite on preheadache scotomas in a subject with migraine. The amount was insufficient to cause a drop in blood pressure or "light headedness."

cerebral blood flow. Symptoms due to cerebral vasoconstriction should be overcome by cerebral vasodilatation in the presence of a sustained normal level of blood pressure, but they should be augmented by a fall in blood pressure with accompanying decrease in cerebral blood flow. The experiments to be described were based on these two potential actions of the vasodilator drug amyl nitrite.

Method.—The subject's preheadache scotomas lasted approximately forty to forty-five minutes. For the most part, visual fields were charted with a standard perimeter, though the subject was sufficiently familiar with perimetric methods to be able to chart his visual fields on an improvised screen. In the absence of scotomas, the subject familiarized himself with the effect of amyl nitrite and pre-

pared for two experiments. 1. He learned to inhale just enough amyl nitrite to induce a head flush without appreciable change in blood pressure. Under such circumstances no "light headedness" or syncope occurred, though slight headache and pulse acceleration did. 2. By rapidly inhaling larger amounts of amyl nitrite he caused a precipitous fall in blood pressure, with "light headedness." Nevertheless, it remained possible for him under these circumstances to define accurately his visual fields. The following results are representative of the two types of experiment.

Experiment 1.—The subject noted a quadrantic defect at 4:45 p. m. (fig. 6). By 5 p. m. this quadrantic defect became a complete right upper quadrantic defect. In the manner just described, a small amount of amyl nitrite was inhaled at 5:01

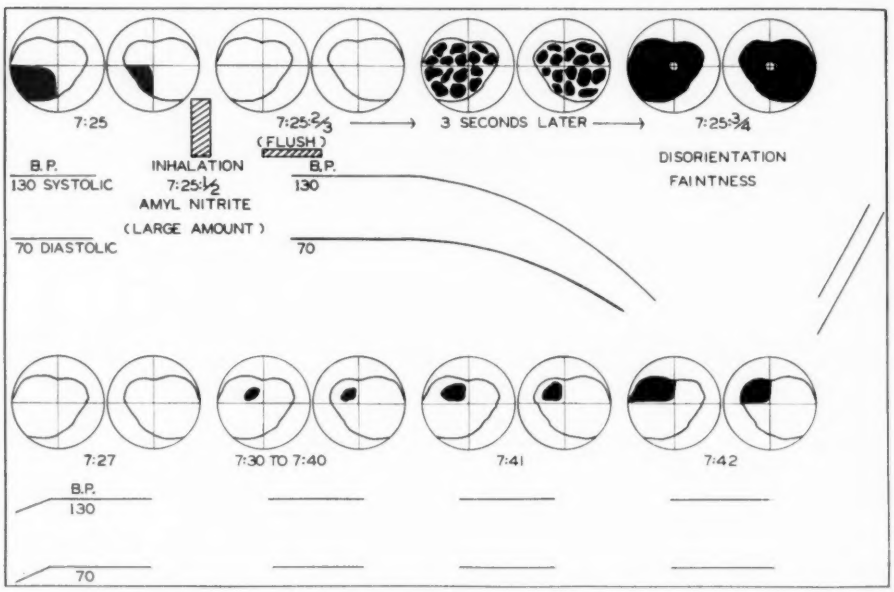

Fig. 7.—Effect of inhaling a larger amount of amyl nitrite on preheadache scotomas. Here a sufficient amount was inspired to cause an abrupt fall in blood pressure, with amblyopia and faintness.

p. m. Fifteen seconds later the subject experienced a flush, and by 5:02 p. m. visual defects had entirely disappeared. The blood pressure, which had been 130 systolic and 70 diastolic, remained approximately the same for the next four minutes. By 5:06½ p. m., or four and one-half minutes after the disappearance of the defect, it began to return, and within a minute and a half the visual defect had returned to its former size. At 5:10½ p. m. the experiment was repeated. Again small amounts of amyl nitrite were inhaled, and fifteen seconds after inhalation came the flush, which was soon followed by complete disappearance of the visual defect. Blood pressure dropped very slightly, and the pulse rate accelerated from 70 to 100. At 5:14½ p. m. the visual defect began to return in the manner indicated in the figure, beginning at the center and progressing peripherally. By 5:15 p. m., or within half a minute, the visual defect had again returned. Examination of the

fundus before and during the visual defect revealed no change in the appearance of the retina or retinal vessels. During the action of amyl nitrite all the retinal vessels were dilated.

EXPERIMENT 2.—The subject first noted a right lower quadrantic field defect at 7:25 p. m. After initial blood pressure readings he inhaled repeatedly and deeply of amyl nitrite. Within ten seconds the subject experienced the flush, and soon thereafter the visual fields became normal. Three seconds later multiple visual field defects became manifest, and within fifteen to twenty seconds of the beginning of inhalation the subject complained of feeling faint and said that only central vision remained. At this point the blood pressure was so low that an accurate reading could not be made. Within about a minute the blood pressure had again risen to 130 systolic and 70 diastolic, the visual fields had again lost all defects and the subject was no longer light headed. Within three minutes a quadrantic defect began to manifest itself—now, however, in the right upper quadrant. Within a minute this had become larger, and within two minutes it obliterated the right upper quadrant (fig. 7).

Comment.—It is apparent from these experiments that cerebral vasodilatation associated with a sustained normal level of blood pressure caused symptoms to disappear, whereas a procedure that decreased cerebral blood flow caused the symptom to become worse. From this it may be deduced that cerebral vasoconstriction was responsible for the visual defect in this patient with migraine. It is also likely that the cause of the visual defect was not in the retina or orbit but within the cranial cavity.

There are several reasons for making the latter inference. First, during an attack there was sparing of central vision. Second, homonomous quadrantic defects could readily result from a single defect in the visual cerebral cortex, whereas it would be necessary to postulate a bizarre arrangement of multiple defects in the retina. Third, the progression of the scotomas from center to periphery also suggests cortical involvement, since such a defect could result from occlusion of the branches of the posterior cerebral arteries, causing ischemia of the most peripheral portions of the artery's blood supply, namely, that area near the occipital pole and spreading ultimately to involve the areas more anterior. If the defect resulted from retinal ischemia the opposite would hold. Hence, it is inferred that visual preheadache phenomena result from dysfunction of cerebral vessels, in contrast to the headache phenomena, which result from dilatation of extracerebral vessels.

It is of interest that the preheadache visual phenomena seldom overlap the headache phenomena, or at most by but a few minutes. This indicates that cerebral vasoconstriction has terminated before extracerebral vasodilatation has begun. It is conceivable, to be sure, that there is also dilatation of cerebral vessels following the vasoconstriction, but it is likely that such cerebral vasodilatation plays but a slight part in the headache.

Vertigo, paresthesias and motility defects occur also as preheadache symptoms in migraine and might also result from a similar dysfunction, namely, vasoconstriction of cerebral (or brain stem) arteries. There is reason to believe from bedside experience with the use of vasodilator agents for the amelioration of preheadache symptoms [9] that the inferences derived from intensive studies on one subject would be confirmed in a larger group.

Further relevant data come from the case descriptions of Adie.[10] He described a series of patients with long-standing periodic headaches preceded by defects in the visual fields. Such defects usually were of relatively short duration and left the patient free from symptoms between attacks. However, in each instance, after years of short-lived attacks, the patient finally failed to recover, and a permanent hemianopic defect resulted. It may be inferred from the data of these experiments that permanent tissue damage resulted either from thrombosis in a constricted cerebral artery or from too prolonged ischemia.

CONCLUSIONS

Histamine headaches were abolished by increasing the intracranial pressure, thereby giving extramural support to the cerebral arteries at the base of the brain. This is further evidence that histamine headaches result mainly from the dilatation and distention of cerebral arteries.

The headaches of migraine were not reduced in intensity by increasing intracranial pressure. This is further evidence that such headaches arise from extracerebral arteries.

Headaches associated with hypertension were not reduced in intensity by increasing intracranial pressure. This is further evidence that such headaches have a similar origin in extracerebral arteries.

Scotomas occurring as preheadache migraine phenomena were demonstrated to result from constriction of cerebral arteries.

The essential migraine phenomena result from dysfunction of cranial arteries and represent contrasts in vascular mechanisms and vascular beds. Preheadache disturbances follow occlusive vasoconstriction of cerebral arteries, whereas the headache results from dilatation and distention chiefly of branches of the external carotid arteries.

9. Oliveira Lima, O.: O problema clinica da enxaqueca infantil, Brasil-med. **53**:765, 1939.

10. Adie, W. J.: Permanent Hemianopia in Migraine and Subarachnoid Hemorrhage, Lancet **2**:237, 1930.

OBSERVATIONS ON REFLEX RESPONSES DURING PROLONGED PERIODS OF HUMAN REFRIGERATION

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In December 1938 one of us (Fay) demonstrated that rectal temperature in the human being could be reduced to 92 F., or below, for many hours without apparent injury to the patient. Since that time more than 62 patients have been subjected to one to six episodes of refrigeration and observed when rectal temperatures were reduced to various levels below 90 F., as far down as 74 F.

Repeated neurologic examinations were made of 42 patients (the service of Dr. Temple Fay) during induced states of refrigeration. These 42 patients were subjected in all to 83 episodes of reduced body temperature, each episode ranging from twenty-four hours to five days in duration. Approximately 400 neurologic examinations were made of the patients in this group.

Each neurologic examination consisted of testing for the following reflexes: jaw jerk, radialis, periosteal, ulnar pronator, biceps, triceps, patellar, ankle, palatal, corneal, plantar, abdominal and cremasteric. The presence or absence of the Chvostek, Babinski and Hoffmann signs and ankle clonus was noted. On patients sufficiently cooperative, various tests for coordination were performed. When possible, the pupils were examined in relation to their relative size, shape and reaction to light and in accommodation. In 1 instance, the gait of a patient with a rectal temperature of 90 F. was observed. Observations were made as to the patient's attention, perception, orientation, reasoning power and emotional state during the period of reduced body temperature.

No recording of any similar neurologic observations on human beings during a state of induced and regulated hypothermia has been noted in the literature, though some work has been done on the effect of cold narcosis in animals.

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Read before the Harvey Cushing Society, Kansas City, May 2, 1940.

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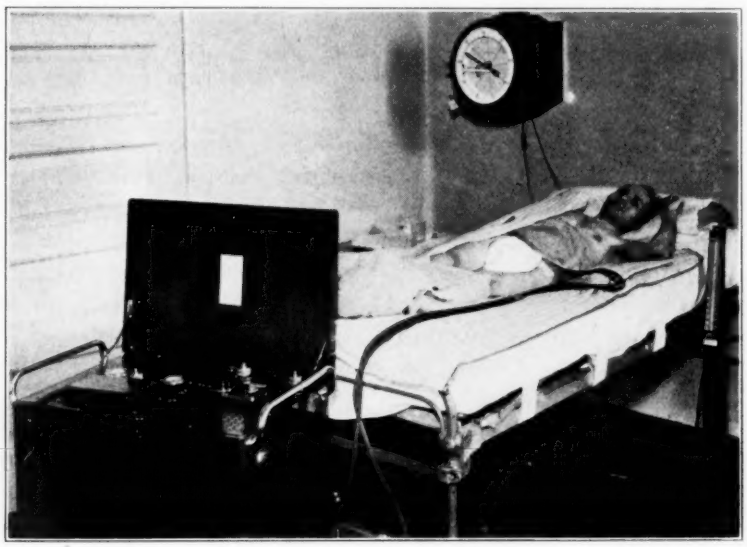
Simpson and Herring,[1] in 1905, in their study of the effects of cold narcosis on reflex action in warm-blooded animals, found that the skeletal muscles became more irritable as the temperature fell; the knee jerk persisted but grew weaker. They showed that during recovery from cold narcosis the first reflexes to appear in the cat were acceleration of breathing, on application of hot water bottles, and winking of the eyelids on gentle stroking of the skin at the inner canthus of the eye. These reflexes, they stated, appeared when the temperature was about 71.6 F. At 75.3 F. the heat-regulating mechanism started to assert itself. Fine tremors and rhythmic movements of the limb appeared, and the pupils began to respond to light at about the same time. The conjunctival



Photograph of patient under general refrigeration, showing thermocouple reading of 82 F., with apparatus used to maintain a state of general hypothermia. Note the blanket containing rubber tubing and coils, through which the refrigeration solution is pumped by a thermostatically controlled machine at the foot of the bed.

reflex was last to appear when the temperature reached 78.8 to 80.6 F., and consciousness and voluntary movements returned soon afterward.

Working with muscular contractions induced reflexly by single induction sparks, Storm van Leeuwen and van der Made,[2] in 1916, found

1. Simpson, S., and Herring, P. T.: The Effect of Cold Narcosis on Reflex Action in Warm Blooded Animals, J. Physiol. **32**:305-311, 1905

2. Storm van Leeuwen, W., and van der Made, M.: Ueber den Einfluss der Temperatur auf die Reflexfunctionen des Rückenmarks von Warmenblütern und Kaltblütern, Arch. f. d. ges. Physiol. **165**:37, 1916.

that the maximum muscular response occurred when the temperature of a spinal cat was about 100.4 F. At a lower temperature, it was constant until a temperature of 95 F. was reached. Below that it diminished regularly.

Cooper and Adrian,[3] in their work on frogs and cats, in 1924, noted that the tendency of the spinal cord to give repetitive discharge to a single stimulus was also decreased by a fall in temperature.

Hamilton,[4] in 1937, in his studies on animals concerned with the effect of hypothermic states on reflexes and activities of the central nervous system, found that progressive descending paralysis of the central nervous system occurred. Higher nervous function, locomotion, voluntary movements, attitudes, equilibration, hearing and sight were lost. Then swallowing, biting and corneal and flexor reflexes were abolished; finally medullary centers were affected, with resultant respiratory failure and death. The responses which were last to disappear, he stated, were the first recovered.

PRESENT INVESTIGATION

In our group, the patients were given a thorough neurologic examination prior to their subjection to a hypothermic state. These examinations were repeated while the body temperatures were at different levels (98.6 to 90 F., 90 F. to 85 F., 85 F. to 80 F. and below 80 F., whenever the temperature fell that low). In all but 3 cases small amounts of avertin with amylene hydrate or evipan (sodium salt of n-methyl-C-C-cyclohexamylmethyl barbituric acid) were used for induction purposes. Three patients were inducted into the refrigerated state by aid of spinal anesthesia. The value of neurologic changes which occurred during the first few hours of hypothermia, when avertin with amylene hydrate or evipan was used as an anesthetic, obviously could not be relied on, as these drugs temporarily suppressed the reflexes and produced pupillary changes. However, after the patient had been in a state of hypothermia for from eight to twenty-four hours, without any additional sedation, it seemed to us reasonable to assume that changes in reflex activity then occurring at different temperature levels might be considered due to the effects of refrigeration (table 1).

From the 3 patients who were inducted into a hypothermic state by the aid of spinal anesthesia important data were obtained relative to their mental changes immediately after application of cold, since no cerebral sedation was given. As the body temperature was lowered these patients

3. Cooper, S., and Adrian, E. D.: The Frequency of Discharge from the Spinal Cord in the Frog, J. Physiol. **58**:209-229, 1924; The Maximum Frequency of Reflex Response in the Spinal Cord in the Cat, ibid. **59**:61-81, 1925.

4. Hamilton, J. B.: Effect of Hypothermic States upon Reflex and Central Nervous System Activity, Yale J. Biol. & Med. **9**:327-332, 1937.

became increasingly more drowsy and slower in their responses. Speech became thick and slurred and the voice tremulous, often taking on a higher pitch. It was also noted that incoordination of the finger movements began soon after the temperature started to fall and became more pronounced as the temperature was lowered.

Fay and McCravey [5] noted that the patients in a state of hypothermia showed a shivering reflex while their rectal temperatures were falling from 97 to 88 F. This shivering reflex was observed in all the patients examined in this series.

The radial, biceps, triceps, knee and ankle reflexes became increased when the rectal temperature was between 98.6 and 90 F. These reflexes became slightly less active when the temperature range was 90 to 85 F.,

TABLE 1.—*Pupillary Reactions of 42 Patients Subjected to Hibernation*

	Before Hibernation	During Hibernation				After Hibernation
		Temperature 98.6-90 F.	Temperature 90-85 F.	Temperature 85-80 F.	Temperature 80-78 F.	
Pupils						
Regular	42	42	42	42	4	42
Irregular	0	0	0	0	0	0
Size						
Miotic	0	0	0	0	4	0
Normal	41	41	41	41	0	41
Mydriatic	1	1	1	1	0	1
Reaction to light						
Normal	42	..	..	..	..	42
Sluggish	..	42	..	..	..	..
Very sluggish	..	..	42	42	..	..
Lost	..	..	..	..	4	..
Reaction to accommodation						
Normal	42	?	?	?	?	42
Lost	..	..	..	..	..	..

but were more active than prior to hibernation. As the temperature fell below 85 F. these reflexes became suppressed and less active than before hibernation. The patients who were examined with temperatures of 80 F. or below showed abolition of all these deep reflexes.

The corneal reflex remained fairly constant and was demonstrated in 4 patients with rectal temperatures as low as 78 F. The gag reflex did not increase at temperatures between 98.6 and 90 F. Below 85 F. the gag reflex became suppressed, and it was abolished at temperatures below 80 F. The abdominal reflex remained constant until the body temperature fell to 85 F., and then it became suppressed and was abolished at a temperature of 80 F. The cremasteric reflex could not be elicited because the testes were drawn tight against the inguinal ring and the scrotum was shrunken to about the size and firmness of a golf ball.

5. Fay, T., and McCravey, A.: Observations on Shivering Reactions During Human Refrigeration, read by title at the Sixty-Sixth Annual Meeting of the American Neurological Association, Rye, N. Y., June 6-8, 1940.

TABLE 2.—*Number of Patients Showing Reflex Changes Before, During and After Hibernation*

	Before Hibernation					During Hibernation															After Hibernation				
						Temperature 98.6 to 90 F.					Temperature 90 to 85 F.					Temperature 85 to 80 F.					Temperature 80 to 78 F.*									
Reflexes †	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Corneal	..	..	42	..	..	..	..	42	..	..	..	..	42	..	..	..	..	42	..	..	..	4	..	..	..	..	7	35	..	..
Gag	..	7	35	..	..	..	7	35	..	..	..	42	..	..	..	12	30	..	..	..	4	..	..	..	..	42	..	..	..	..
Chvostek	42	..	..	..	..	42	..	..	..	..	42	..	..	..	..	42	..	..	..	..	4	..	..	..	..	40	..	..	..	2
Hoffmann	40	..	..	..	2	30	..	..	..	12	30	..	..	..	12	40	..	..	..	2	0	..	..	..	..	5	5	32	..	..
Ulnar	5	5	32	..	..	2	..	..	40	..	2	..	..	40	..	8	20	14	..	..	4	..	..	..	..	8	10	20	4	..
Radial	8	10	20	4	..	4	..	8	30	..	4	..	4	34	..	11	18	13	..	..	4	..	..	..	..	6	12	22	2	..
Biceps	6	12	22	2	..	4	..	6	32	..	4	..	8	30	..	10	24	8	..	..	4	..	..	..	..	4	16	18	4	..
Triceps	4	16	18	4	..	4	..	7	31	..	3	..	6	33	..	11	28	3	..	..	4	..	..	..	..	15	2	20	5	..
Abdominal	15	2	20	5	..	15	2	20	5	..	15	2	20	5	..	25	15	2	..	..	4	..	..	..	..	..	..	17	..	..
Cremasteric	..	..	17	..	..	17	..	..	..	..	17	..	..	..	..	17	..	..	..	..	4	..	..	..	..	18	10	18	4	2
Knee	18	10	18	4	2	6	..	4	30	2	8	..	12	20	2	10	30	2	..	..	4	..	..	..	..	6	8	20	6	2
Ankle	6	8	20	6	2	4	..	4	32	2	4	..	18	18	2	8	30	4	..	..	4	..	..	..	..	40	..	..	..	2
Babinski	40	..	..	..	2	40	..	..	..	2	40	..	..	..	2	40	..	..	..	2	..	..	..	..	..	40	..	..	..	2
Clonus	40	..	..	..	2	34	..	..	..	6	34	..	..	..	6	40	..	..	..	2	..	..	..	..	..					

* Only 4 patients were observed whose body temperature was below 80 F.

† 0 indicates absence of reflexes; 1 denotes decreased, 2 normal, 3, increased and, 4 greatly increased reflexes.

A positive Hoffmann sign was obtained bilaterally in 12 patients in the group who had temperatures ranging between normal and 85 F. Below this level the sign disappeared, except in 2 patients who showed a positive Hoffmann sign prior to induction of the hypothermic state. Two patients showed a positive Babinski reaction before hibernation. This reaction remained present throughout the period of hibernation. In no patient in the group did a positive Babinski reaction develop while in hibernation. Ankle clonus occurred in 4 patients between temperature levels of 98.6 and 85 F. and then disappeared below 85 F. Two patients who had ankle clonus prior to hibernation continued to have a positive clonus throughout their hypothermic state.

The pupils remained equal and normal in size and reacted to light stimuli at temperatures ranging between 98.6 and 80 F. (table 2). However, as the temperature was lowered the light reflex became progressively more sluggish, until at a temperature of 80 F. four seconds was required for the pupils to reach their maximum contracted state after light stimulation. At temperatures below 80 F. the light reflex became lost. Tests for accommodation could not be accurately performed.

As the body temperature was lowered, the muscles of the extremities assumed a waxy stiffness and when percussed contracted slowly, with subsequent slow relaxation and return to their normal contour. Spontaneous myokymia was observed in patients with temperatures as low as 84 F.; if the phenomenon was not present at this temperature level, it occurred when passive motion of a joint was made.

The patients assumed a characteristic posture denoting cold, with arms held close to the sides and hands against the upper portion of the chest and beneath the chin.

The upper and lower extremities assumed a flexed position, and considerable effort was required to extend them. In a strong patient, it was frequently difficult to extend the arm sufficiently to take blood pressure readings. The wrists were flexed; the hands did not form the fist position but took a "clawlike" attitude. The metacarpal-phalangeal joints remained extended, though the interphalangeal joints remained flexed. The patients attempted to curl up into a ball during the shivering phase. When the rectal temperature was reduced below approximately 88 F. shivering ceased and the patients were comparatively comfortable, though not relaxed, for the increased muscular tone remained.

All volitional movements became progressively slower and incoordination gradually more pronounced as the body temperature continued to fall. A strong man, with a rectal temperature of 90 F., pushed the nurse aside, climbed out of bed, walked in a staggering, ataxic manner across the room, opened the door and was on his way down the corridor when intercepted.

With the body temperature at approximately 85 F. the patients require fifteen to thirty seconds to perform the routine finger to nose test for coordination. The slowed hypertonic movements of the parkinsonian state are simulated, though the incoordination noted here was more pronounced. No athetotic, dystonic or choreatic movements were observed in any patient in the series.

At a rectal temperature as low as 93 F. the patients were fairly alert, comfortable and oriented in all fields and showed no loss of memory for remote or recent events or evidence of any emotional instability. As the temperature was lowered cerebration became more retarded and perseveration of speech ensued. With a body temperature of 82 F. they were able to respond to simple commands, but all responses were delayed considerably. Dysarthria developed at 92 F., associated with a high nasal and tremulous type of voice. Gradually, the dysarthria became more noticeable as the temperature fell to around 82 F. With the temperature between 80 and 82 F. the patients were often unable to say a word, but grunted when asked a question. When the rectal temperature fell below 80 F. vocal response was elicited with difficulty and in only 1 instance did conversation persist (temperature at 74 F.).

Four patients were studied during periods when the rectal temperature was below 80 F. The pupillary reaction to light became abolished, although the corneal reflex remained intact. Supraorbital pressure produced wincing, and these patients would turn the head in an effort to free themselves from discomfort.

Yawning was frequently noted at these reduced body temperatures. The deep reflexes of the extremities became lost at approximately 78 F., along with abolition of the gag and abdominal reflexes.

As the body temperature was elevated the deep and superficial reflexes, which were abolished at a temperature level approximating 78 F., reappeared, though they remained suppressed until the body temperature rose to about 80 F., when they again became exaggerated. At a temperature of somewhere near 97 F. the deep reflexes again became normal.

Repeated neurologic examinations of the patients in this series, following their period of hypothermia, showed no evidence of any permanent reflex change. The patient's reflex activity resumed its normal status. Patients who experienced several episodes of hibernation showed consistent reflex changes each time hypothermia was induced.

In every instance retrograde amnesia existed for the period corresponding to that of refrigeration. Although memory and reasoning powers are retained during the period of refrigeration, not a single patient has been able to recall later, under normal temperatures, incidents arising while under refrigeration, when the rectal temperature was reduced to 92 F. or below.

SUMMARY

Neurologic studies were made on 42 patients during a state of reduced generalized body temperature. These patients received a total of 83 periods of refrigeration. Each period varied in duration from twenty-four hours to five days. Approximately 400 neurologic examinations were made on the patients in this series.

Increase in deep reflexes was found when the body temperature was between approximately 97 and 85 F. At that range of temperature no change in the abdominal reflex was noted. The period of hyperreflexia corresponded closely to the shivering stage. Abolition of deep tendon, abdominal and gag reflexes occurred when the body temperature approached 78 F.

The pupils remained equal, regular and normal in size throughout the hypothermic period, but response to light stimuli became progressively more sluggish as the body temperature was lowered. The light reflex became abolished at 78 F.

Dysarthria began at a temperature of approximately 93 F., and response to the spoken word became practically nil below 80 F.

Cerebration was progressively delayed with reduction of body temperature. Mental faculties were fairly well preserved until the body temperature approached 93 F.

Retrograde amnesia was present for the period the body temperature remained below 92 F.

Appreciation of pain, heat and cold perception was not lost during or after refrigeration.

The symptom of pain, if present prior to refrigeration, was completely relieved in all but 2 instances (4.7 per cent).

No permanent alteration of objective neurologic responses resulted from hypothermia.

MEMORY DEFECTS DURING METRAZOL THERAPY

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Memory defects resulting from metrazol therapy have been commonly observed. It is our purpose to detail the nature of these defects, to record their frequency, to indicate a possible connection with dosage and also to consider the mechanism producing impairment of memory and its relation to therapeutic results. We record pronounced memory defects in 4 cases and less marked changes in 20 others.

REPORTS OF CASES

CASE 1.—*A woman aged 66 with agitated depression of two months' duration. Two previous depressions. Recovery after eight metrazol convulsions; development of confusion and marked memory defect. Recovery from amnesia three months later, with return of depressive trends.*

Mrs. M. K., referred by Dr. A. J. Rosanoff in November 1938, was suffering from depression and agitation associated with self-accusatory ideas of a sexual nature. There had been two previous attacks. After the birth of a son in 1890 she was melancholic for two years, and again in 1912 became depressed and was in and out of sanatoriums until 1918-1919.

Serious tensions preceded the present attack, which began in September 1938. There had been acute financial reverses and the shocking news that the patient's blind son was being sued for divorce.

The systemic, past and family histories revealed no pertinent data. The early personal history was lacking. Apparently, the patient had been pampered by both her parents and her husband, who was fifteen years older than she. She was not in love with her husband. Ten years ago they separated for one year. She was described as very young for her years, and even at the age of 60 enjoyed parties, drinking, smoking and flirting with men. Extramarital affairs were admitted. She was very sensitive, resented criticism, readily lost her temper and was cyclothymic, though usually happy, outgoing and energetic. She was meticulous as to person and belongings and very punctual.

General physical examination revealed wrinkled, inelastic skin, sclerosis and tortuosity of the brachial arteries, arcus senilis and slight beading of the retinal arteries and arthritis of the fingers; the blood pressure was 155 systolic and 85 diastolic, the pulse rate 92 and the weight 104 pounds (47.2 Kg.). Other findings, including the results of neurologic examination, were normal. The electrocardiogram showed left axis deviation. The results of urinalysis, the blood count and the Wassermann reaction of the blood were normal.

The patient was tense, with anxious facies, disheveled hair and untidy clothes; she was seated bent over, picking and crying or talking incessantly. It was impossible to obtain sufficient cooperation for adequate mental examination. Speech was limited to the persistent repetition of monotonous phrases: "That brings me

to awful things in my life. Oh, I hate to talk of them—oh, I have terrible nights! I did horrible things, many of them. Different men, you know, in my life." Although the patient was markedly low in spirits, there was no suicidal trend. There were feelings of guilt and horror as to previous sexual escapades, fellatio included. She felt contaminated and thought she had syphilis. The sensorium test (not performed until three days after the first metrazol convulsion because of inability of the patient to cooperate) gave normal results except for a reduced memory span (5 digits forward and 4 digits backward) and poor calculation (inability to give 3 per cent of 200 or to subtract 7 from 100). Lack of attention may have been a factor. Insight was present. The diagnosis was agitated depression of manic-depressive psychosis.

Eight metrazol treatments, all of which resulted in convulsions, were given as follows:

Date	Nov. 1938	8	11	14	17	21	25	Dec.	1	5
Amount of metrazol (cc.)		4	4.6	4.8	5	5	5		5.2	5.2

Improvement set in with the first convulsion. Three days later the patient said: "The night before last was the first night that I seemed a little like my old self. I could let go a little from my vile thoughts. Oh, they were so terrible!" The patient was less agitated and smiled. Improvement was rapid. A note made on November 28, before the seventh injection, stated: "The patient is much improved; she is no longer depressed and laughs heartily. She admits improvement begrudgingly and appears absorbed in her own thoughts." She complained: "You know there may be something wrong with my memory. There may not be. I'm having trouble thinking of what did happen this morning. I must have had breakfast but I can't tell what—I'm just trying to think." She had had no breakfast, and the memory span was 6 digits. She crossed out *e*'s on a printed page without error. She was given two further treatments as reenforcement. She went home on December 5, for economic reasons, having received her eighth injection that morning.

When she returned three days later for examination, the agitated depression was entirely gone. She was confused, however. Her husband reported: "She appears entirely well except for poor memory. She forgets from one minute to the next. She also sits around dazed at times. She sleeps well and eats heartily." She did not remember her homecoming dinner on the next day and even complained of her children not coming to see her. When reminded of their visit the night before, she asked where they sat and what they talked about. She finally accepted the explanation without recalling the visit.

On examination the patient was quiet, smiling too readily, with her eyes downcast; she would flick her finger nails as in her absorption she tried hard to express answers to questions. At times she turned to her husband for help. The sensorium was considerably impaired. The patient could not recall the day of the month, the name of the doctor or that of the sanatorium. Recent memory was impaired for the events at the sanatorium immediately preceding her going home. She gave her age as 72 (actually 66). She could not recall how long she had lived in Iowa or the time spent in different cities in southern California. The digit span was 5 forward and 4 backward. She could not subtract 7 from 100 or give 3 per cent of 200. She gave correctly two of the three largest cities and named only Roosevelt when asked for the last five presidents. She could not differentiate character from reputation. Insight was fair.

It was apparent that the patient had a marked memory defect due to the treatment. Attempts to make contact with her subsequently were not satisfactory, as she had acquired a fear of the treatments. Telephone communication on the tenth

day after discharge revealed that the patient still had marked memory defect, but already definite improvement had been noted and no other symptoms had returned. The family stated that the patient's memory gradually returned to normal over a period of three months, but at the end of this time depressive symptoms again began to make their appearance. Examination of the mental status was again performed eight months after treatment, in August 1939. The patient was depressed, though there was less agitation than on the first admission. The sensorium was normal. The digit span was 7 forward and 5 backward.

In this case, then, a patient after six injections lost her symptoms and after eight treatments showed a pronounced memory defect, persisting for three months, after which the depression returned.

CASE 2.—*A man aged 40. Depression with ideas of reference and persecution. Suicidal thoughts. Eight metrazol convulsions. Development of marked sensorium defects. Silly behavior and perseveration, which disappeared after cessation of treatment.*

F. H., referred by Dr. H. C. Epstein, entered the sanatorium on July 17, 1939, after an illness of two months. The systemic and past histories were negative except for mild drinking and unilateral blindness due to trachoma in childhood.

Physical examination revealed a fast pulse (120), slight rhinophyma with impaired sensation to pinprick over the nose, keratitis on the left side and pyknic habitus. The results of neurologic examination was negative.

The personal history revealed that the patient's mother died in his infancy and that the father was a drunkard. The discolored blind eye gave him a marked inferiority complex. He had apparently been well adjusted at an orphanage, where he remained until he completed grammar school. After this he was always self sufficient, working hard at unskilled jobs. He maintained himself in moderate comfort, without provision for the future.

Sexual experience, probably not in excess of twelve contacts altogether, had been limited to prostitutes. Masturbation presented no special problem. There had been few "crushes." Four years ago the patient was betrothed, but broke the engagement because his fiancée was "too bossy." He had no hobbies; was sociable with both sexes; was sensitive, resentful of criticism, cheerful most of the time, conscientious, generous and kind; a doer rather than a thinker; energetic and a good mixer, but apparently did most of the menial work at parties; meticulous as to details; punctual; interested in politics, and a good Catholic.

The patient was depressed and slightly retarded in both speech and activity. He was well groomed and cooperative and presented no mannerisms. He expressed the belief that every one was looking at him and that the radio broadcast about him as he was a great public enemy. He said: "I'd better kill myself if things keep on this way." He stared into space and said that the world looked black and that he was guilty of some unknown crime, so that he must surrender to the police. Sensorium tests revealed no special defects, and the auditory memory span was 8 digits forward. There was probably some superficial insight. The patient was perplexed, admitting that he might be mistaken about the actuality of his delusions.

The diagnostic impression was manic-depressive psychosis, with a few schizoid features.

Eight metrazol convulsions were given between July 22 and August 10. After the first injection delusions were no longer expressed, and after the fourth treatment the patient was apparently normal. After the seventh treatment the patient encouraged the advances of a hypomanic girl, smiling in a silly manner, which behavior his family reported as foreign to his normal self. Also, he permitted his beard to grow and failed to bathe.

After the eighth treatment the patient seemed confused; therefore the sensorium was rechecked on August 11. The patient was oriented as to time, person and place. Recent and remote memory appeared intact. The memory span was reduced to 6 digits forward and 4 backward. Only 1 of 3 items was recalled after five minutes, and this inaccurately. He failed on problems in simple subtraction and multiplication. He named three of the last five presidents and could not name the mayor and governor. All of these tests he had previously passed.

On August 18 the family reported that normal behavior had returned. The patient was in fine spirits, and his memory was good. The sensorium was normal on testing; however, the auditory memory span was 7 digits forward, whereas it had been 8 digits before metrazol therapy.

CASE 3.—*A woman aged 54, with agitated depression of two months' duration. Two attempts at suicide. After five metrazol injections (third convulsion), given over a five day period, some lessening of depression but development of marked confusion, followed by pronounced loss of memory. Recovery with cessation of treatment. Cautious resumption of treatment, with subsequent complete recovery without residual memory defect.*

S. H., a Caucasian woman aged 54, was referred by Dr. Le Grande Hall on May 11, 1939. She had consulted him two months previously because of urinary frequency and vaginal discharge. The pyelitis and atrophic vaginitis responded promptly to medical therapy. Definite mental symptoms began two weeks before we saw her. She became worried unduly over losing some papers which belonged to her club. She accused herself of falsifying matters in arranging her mother's old age pension and complained that she could no longer attend to her household duties.

Insomnia had troubled her for several years but had been pronounced for two months. She now cried easily, tired readily and had two loose bowel movements daily. On the other hand, her appetite was good, and she had lost no weight. Backache and arthritis of the fingers had been present for years. She complained that her speech had "grown sad." There was a past history of typhoid fever in 1902, complicated by pneumonia, with a temperature of 106 F. and delirium; peritonitis after removal of abscessed tonsils, in 1917, and hysterectomy, in 1928. Two cousins had had psychoses of undetermined type, with recovery.

The results of neurologic examination were normal except for marked tremor of the hands. Physical examination revealed deformity of the fingers from arthritis, inelasticity of the skin and hands, obesity, a temperature of 98 F., a pulse rate of 124 and blood pressure of 165 systolic and 100 diastolic. Results of urinalysis, the blood count, the Wassermann reaction of the blood, roentgenograms of the gastrointestinal tract and kidneys and the electrocardiogram were all normal.

The personal history was not unusual in respect to birth and early development. The patient was a happy, robust child, without neurotic stigmas. She was an honor student and well adjusted at school. Her sexual history revealed no tensions. She married at the age of 18. She was a leader in church, club and community affairs; was serious minded, not worrisome, sensitive, of even temperament, usually happy and very energetic; had many friends; was kind, overly generous, very conscientious, honest and idealistic, and was not prudish, meticulous or punctual.

When first seen, the patient was markedly agitated and depressed, whining and continually blaming herself. The personal appearance showed neglect. Continuous preoccupation with her depressive trend prevented complete mental examination. "I just keep wondering why I did certain things. I try to pray, but I can't. Everything is so far away from me. I read a little paragraph, and then I don't remember it. I can't see how this will clear up all my mistakes." She bemoaned the trouble

brought her husband because of her inability to assume responsibility. "I used to be able to do social service work, and that's what hurts me so." Many bad dreams lately were admitted. She bathed several times daily because it made her feel better. On occasion she bumped her head repeatedly on the bathtub, and one evening she tried to take an excessive amount of a sleeping potion. She expected never to see her family again and was sure that her mother-in-law had died the day before.

The patient was oriented. Recent and remote memory were fair. Three test items were not recalled after three minutes. The memory span was 5 digits forward and 3 backward. In calculation, the patient knew that 7 times 8 is 56, but could not give 3 per cent of 200 and said she was too disturbed to go ahead with serial subtraction of 7 from 100. She was out of contact with current events but showed a fair degree of insight.

The diagnostic impression was manic-depressive psychosis (agitated depression).

The patient was admitted on May 11; though obviously depressed and tense, she was quiet. On May 12 she was acutely excited, with rapid respirations, dilated pupils and staring eyes. She accused herself of killing half the people of Los Angeles, thought it was all in the newspapers, felt she had disgraced her family and asked why did they not tell her she was a "mental case." On the next night this recurred. Then she remained acutely disturbed about thirty-six hours, before metrazol treatment was instituted. Incidentally, she received 3 grains (0.195 Gm.) of pentobarbital sodium on the night of May 14. During the premetrazol period the temperature remained normal and the pulse rate ranged from 100 to 124.

Treatment Notes.—May 15: The first metrazol injection (4 cc.) failed to produce a convulsion. A second injection (5 cc.), several minutes later, resulted in a strong generalized convulsive reaction. On awakening the patient smiled quietly and held the doctor's hand. She was agitated and depressed again later the same day. That night she tried to tie a sheet about her neck and attempted to hurtle out of bed head first.

May 17: The patient was noisy and excited during the night. She smiled on seeing the doctor and said she felt a little better. A third metrazol injection produced a second convulsion.

May 18: The patient was friendly. She asked whether "persecutions and things said" about her were imaginary. She showed a tendency to doubt delusions and ideas of reference and blamed herself for many fictitious wrongdoings.

May 19: She was markedly agitated. She pounded her eyebrows during the night so that they were black and blue. She smiled at times in a strange manner during agitation. She kept talking of a need to attend two funerals. She took continuous tub baths.

May 20: A fourth metrazol injection (5.4 cc.) failed to produce a convulsion. Several minutes later a generalized convulsion was obtained with 6 cc. of metrazol (fifth injection, third convulsion). After this treatment the patient was markedly disturbed. She was suspicious of proffered orange juice. Her temperature rose to 101 F. (previously normal). Her pulse, which since the onset of metrazol treatment had dropped to between 76 and 94 per minute, rose to 124 at 12:30 p. m. She was actively hallucinating. "Your suit is burning. All the securities are being burnt up." She was self depreciatory. She was given 20 units of insulin buffered with carbohydrates, in an attempt to control the agitation.

May 21: The patient was less agitated but was confused and delusional. She occasionally answered questions lucidly. The temperature was 99.6 F.

May 22: The patient passed a poor night and was hyperactive, restless and terrified. "Don't call the police." Insulin, 30 units, buffered with carbohydrates was given. Writing showed perseveration and consisted of irregular scribbling

across the page of isolated letters and a few single words. "Bigamy" appeared twice and a number of B's. She had moments of near lucidity, and occasional smiling was noted.

May 23: The patient had a poor night. Thirty-five units of insulin buffered with carbohydrate was given. She showed less restlessness. She was delusional, though she spoke normally to her family for a few minutes.

May 24: The patient had a good night. She was quiet and markedly depressed, with feelings of guilt. A sixth metrazol injection was followed by the fourth convulsion. The patient was very restless that night and was confused. She tried to get out of bed.

May 25: The patient was depressed. She dressed and fed herself. She had a quiet day.

May 26: She had a quiet night. Forty units of insulin buffered with carbohydrate was given. She sighed frequently and smiled occasionally. "I hope my mind comes back. I just can't think." Speech was rational.

May 27: She had a quiet night. Forty-five units of insulin buffered with carbohydrate was given. She noted the limitation of clothes. "Life is so hard. It is for everybody." That night she was restless again and pulled her hair.

May 28: The patient complained of insomnia, backache, abdominal pains and feeling of weight on the head. After a massage, she said: "That's good." Her husband and family physician reported her behavior as the best in months but noted impaired memory.

May 29: She complained of terrifying dreams. Forty-five units of buffered insulin was given. She did not remember when her husband visited her. "A man came to see me. They said he was my husband." She was cooperative and went out in the yard.

May 30: She was depressed. "The wages of sin are death." "If I could only go." She complained of fatigue. The sensorium was markedly impaired. She was disoriented as to time (day, date and year) and place. She did not know the doctor's name and could not recall items of breakfast. She knew her own address and telephone number. She could not tell who was the president or what city was the capital of the United States. She could not tell the difference between a lie and a mistake.

May 31: She was still depressed and disoriented for time and place. There was tremor of the hands. She said she had been at the sanatorium two months. She gave correct answers as to the president and the capital of the United States. She knew she was in California but could not name the governor or mayor. She knew that New York and Chicago are the largest cities. The memory span was 6 digits forward and 3 backward. She recalled correctly the name of the sanatorium and the year five minutes after being told.

June 1: She was more cheerful and hopeful of recovery. She gave the correct date and the name of the sanatorium.

Although the memory was still somewhat impaired, the patient continued to be cheerful until June 5, when the depression again appeared to be getting more marked. Metrazol treatment was therefore continued but was administered more cautiously than previously, at longer intervals of twice a week. Favorable progress continued, the depression becoming less tenacious and lifting more with each treatment and the sensorium gradually clearing.

June 12: All sensorium tests gave normal results except for a mild memory defect. There was no recall for three items after five minutes. She did not recall early suicidal attempts. The memory span was 6 digits forward and 5 digits backward. She had no knowledge of current events. Calculation was satisfactory

only with pencil and paper. Insight was present. Beginning on June 17, cheerful days became the rule rather than the exception.

June 28: The patient was symptom free except that she cried easily. She was in good spirits. "I am normal again." She said she felt better than ever before in her life, but complained of poor memory. Complete sensorium tests gave normal results except for a digit span of only 6 digits forward and 5 digits backward. Five mistakes were made in serial subtraction. She still was not in touch with current events. She became tremulous in company.

June 29: The eleventh metrazol convulsion was induced by the fifteenth injection. The patient was sent home.

July 8: She was symptom free except for nervousness when in company and mild memory defect. She had taken charge of the house and was again active. She had difficulty in recalling events of sanatorium days and in naming the women of her club. She said her memory was improving. She was informed on current events. The digit span was 7 forward and 4 backward. She was given a treatment and was to have another on July 10.

July 25: The patient was "normal" up to one week before this date. Since then, she had had feelings of self depreciation and did "not smile the way she did before." She complained of being upset by company. A convulsion was induced with 9 cc. of metrazol.

July 28: Her condition was the best it had been. She was cheerful, went out to dinner and enjoyed it. She settled some business affairs and wrote letters to friends. She had her fifteenth (last) convulsion, induced with 9.2 cc. of metrazol.

November 19: The patient was in good spirits, and had returned to all her previous activities and duties. There was no impairment of memory. The memory span was 8 digits forward and 6 digits backward.

Summary.—A patient with agitated depression and clear sensorium presented some difficulty in testing because of agitation and preoccupation. At the outset of treatment, she had three metrazol convulsions, at two day intervals, but received in addition two injections of metrazol which did not result in convulsions. After this there developed definite confusion, disorientation, visual hallucinations, apprehension and marked disturbance at night. When this cleared, marked sensorial impairment was evident. At first, the metrazol treatment only temporarily or intermittently ameliorated the depression, confusion supervening. With cessation of treatment, the defects in sensorium tended to clear while the depression recurred. Metrazol treatment was therefore resumed cautiously, at less frequent intervals. Recovery, with the return of normal sensorium, occurred. The amnesic syndrome is presumably a toxic effect produced by frequently repeated injections of metrazol.

CASE 4.—*A man with paranoid schizophrenia of one month's duration. Recovery, with complete insight and ability to resume previous occupation after three months' treatment with insulin (sixty-two shocks). Relapse with development of "larval" symptoms after three months. Recovery under metrazol treatment. Inability to play Chinese checkers or count a badminton score (recently acquired functions) after twelve metrazol treatments.*

This case has previously been reported.[1]

Analysis of the effects of metrazol treatment in 32 other cases reveals that mild memory defects were present in 20 instances. The incidence here is lower than usual, since we did not search for the memory defect in the earlier cases and tried to avoid this complication in the later cases. The memory defects were usually for isolated, minor events of recent origin. It was uncommon to find a

1. Ziskind, E., and Somerfeld-Ziskind, E.: Loss of Recently Acquired Memory Due to Metrazol Therapy, Bull. Los Angeles Neurol. Soc. **4**:77 (June) 1939.

defect in remote memory. Frequently either the patient or the relatives will note the failure to recall an event which occurred just prior to coming to the sanatorium, or shortly after, but preceding the onset of therapy.

One patient wondered when her son had obtained his new car, whereas before treatment she had complimented him on the transaction. A second patient forgot the long automobile trip she had made just prior to treatment. Another failed to recall how the rooms of her recently acquired apartment were furnished. Still another patient complained of inability to recall the color of last season's hat. One patient's father, a physician, said that his son forgot that he wrote a thesis on insurance medicine a month or so before. Another patient under treatment failed to recall that after visiting the dentist she stopped at home, on the way back to the sanatorium. These examples indicate the common defects. As a rule, the mental status shows no other abnormalities. The patient may or may not recognize the details of forgotten material when recited to him. One patient, a physician, knew that roentgenograms of his spine had been taken, but even to this date he cannot recall the trip to and from a neighboring hospital or the actual taking of the pictures.

COMMENT

Nature of the Memory Defect.—Persistent amnesia resulting from metrazol therapy resembles the memory impairment noted in "organic psychoses." In the mildest form, there is a lacunar disturbance for isolated events of recent origin. When the severity is greater, remote memory is also affected. Still more pronounced forms present the Korsakoff syndrome. Other abnormalities in the more severely affected patients are impaired sensorium, silliness, neglect of personal appearance, mental retardation, emotional lability, perseveration and feelings of familiarity. These associated symptoms, analogous to those observed in psychiatric pictures due to lesions of the brain, are significant, since they are readily recognized as being due to the treatment and not as part of the original disease.

Memory defects may be overlooked, particularly in patients with variable degrees of inaccessibility. The memory impairment with or without the other associated symptoms may give the impression that the patient is getting worse and lead to the discontinuance of treatment. Such practice will give rise to therapeutic failures and has probably colored statistics unfavorably. For satisfactory continuation of treatment, the physician judiciously spaces subsequent injections farther apart. In fact, our experience indicates that shock therapy is highly quantitative and that success or failure may depend on adequate spacing of convulsions with reference to the favorable effect on symptoms, on the one hand, and the adverse impairments in memory, on the other.

Platner [2] and Müller [3] have reported the Korsakoff syndrome as a complication of shock therapy. Platner expressed the opinion that

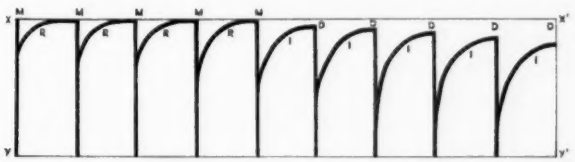
2. Platner, P.: Korsakoff Syndrome After Insulin and Metrazol Treatment of Schizophrenia, Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:728, 1938.

3. Müller, M.: Insulin Therapy of Schizophrenia, Am. J. Psychiat. (supp.) **94**:5 (May) 1938.

metrazol is a greater offender than insulin. This conforms with our experience. Tooth and Blackburn,[4] Diez Canseco [5] and Low and his associates [6] recorded less serious memory defects, chiefly for items of recent memory and retention. Memory impairment may be transient or persistent, even for months. Recovery tends to occur but occasionally may not be complete. In all of our cases full memory did return.

Genesis of the Memory Defect.—There is pronounced impairment of memory after each metrazol convulsion which is brief and transient [7] (possibly entirely reversible for one or more of the early seizures). After the later convulsions minor residual memory defects may persist and cumulate finally to produce the more enduring amnesias.

This development may be visualized as a resultant of two forces, the primary destructive or depressive effects of metrazol on neural functions and the secondary recuperative, nutritive or anabolic powers of the brain. The primary action of each metrazol convulsion is shown (see figure) as a precipitate diminution or depression of memory ^{M}. This corre-



Curve showing memory defect during a series of metrazol convulsions. *X-X* indicate the level of normal memory; *Y-Y* the level of complete memory loss.

sponds with the period of unconsciousness and subsequent confusion. The recuperative phase ^{R} then sets in, and the loss of function is

4. Tooth, G., and Blackburn, J. M.: Disturbance of Memory After Convulsion Treatment, Lancet **2**:17 (July 1) 1939.

5. Diez Canseco, F. F.: Abnormalities of Memory in Schizophrenic Patients Treated with Metrazol, Rev. neuro-psiquiat. **1**:150 (June) 1938.

6. Low, A. A.: Question Box, Psychiatric Exchange Illinois State Institutions, January 1938, vol. 1, p. 33. Low, A. A., and Lukins, N. M.: Shock Treatments for Psychotic Patients and Their Relationship to Occupational Therapy, Occup. Therapy **18**:85 (April) 1939.

7. Diez Canseco [5] gives the duration as being up to two hours, and Wittman (Psychological Study of Mental Confusion Following Metrazol Therapy, Elgin State Hosp. Papers **3**:67 [Jan.] 1939), up to eight hours. We should expect the duration to become progressively longer as the injections become more numerous and more frequent. Cohen (Return of Cognitive Conscious Functions After Convulsions Induced with Metrazol, Arch. Neurol. & Psychiat. **41**:489 [March] 1939) has recorded the sequence of recovery for other mental functions besides memory in the postconvulsive period. The postconvulsive amnesia is chiefly for events of recent origin. When the patient wakens from the postconvulsive stupor he shows loss of memory principally for the occurrences of the same morning. Recovery takes place progressively, so that the earliest happenings of the day are recalled first and then subsequent events in order up to the time of the injection. The injection itself is recalled last.

shown to be reversible. With repeated injections, the functional loss is recovered from more slowly and incompletely [I], and residual impairment [D] persists at the end of the interval of treatment. The residual defect increases with repeated treatments and tends to become more pronounced and of longer duration, until finally it may be permanent. There is probably actual injury to nerve cells, the damage being reversible in early, or milder, stages and irreversible in the later, or more pronounced, states. In fact, this genesis of the memory defect holds for some other types of damage to the brain resulting in loss of normal function with either metrazol or insulin, in which the destruction, if severe enough, may lead even to decortication and decerebration. If the proffered interpretation is correct, the persistent amnesias are but the cumulative, more enduring residuals of the acute postconvulsive memory impairments.

Relation of the Amnesia to the Mechanism of Shock Therapy.—Similarities in the loss of mental symptoms and the loss of memory under treatment suggest a common underlying mechanism. The clinical similarities are:[8]

1. Both mental symptoms and memory tend to become effaced as the therapy progresses. The effect on the symptoms is greater in degree and earlier in occurrence than that on the memory.[9] This is in conformity with the complete loss of symptoms after therapy, at which time memory, as a rule, is but little affected.

2. The fluctuation in symptoms and memory is essentially similar after individual treatments. As with memory, there is an early transient postconvulsive loss of symptoms. The acute temporary disappearance of the depression, and even displacement by elation, is not infrequently noted after a metrazol seizure.

A dramatic instance of this sort occurred in a depressed patient who for three weeks showed extreme restlessness and thrashing about, so that serious exhaustion was feared. The first injection of metrazol failed to produce a convulsion, but for about three minutes all movement ceased and a smile broke out on the previously depressed, tense face.

With each subsequent treatment the relief from symptoms (like the arrest of memory) is progressively greater and longer.

The transient character of the improvement at this stage is at times apparent to the patients themselves. A patient said three days after her fourth convulsion:

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8. Reference to therapy is limited to the manic-depressive depressions, since it is here that one sees the response to metrazol most easily and constantly.

9. The greater vulnerability of the symptoms is probably to be correlated with their pathologic (unstable?) substratum and their more recent development, as contrasted with the normal anatomicophysiologic character and greater longevity of the memory processes. Based on these considerations, a test for prognosis has been devised and is being studied.

"Each time after a treatment I get better and then I slip back. Oh, I had such a good day yesterday and the day before. I was well. But now I am so depressed because today I am beginning to feel the way I did before."

Soon the symptom is gone for the intertreatment interval of two to four days. Cure is suspected, but the depression may recur if the treatments are terminated. Finally the symptom disappears completely and permanently. (The parallel memory defect would be the persistent Korsakoff syndrome.)

This sequence in the loss of symptoms (substitute *S* for *M* in the figure) is the counterpart of the patient's loss of memory. Therefore a common underlying mechanism (readily recognized as physicochemical for the memory defect) is suggested for the therapeutic results and the amnesia. Fortunately for therapy, in the early forms the abnormal functions of the nervous system (symptoms) are more vulnerable than the normal functions, such as memory.

Relation of Memory Defect to Dosage.—The degree of memory defect is in proportion, among other things, to the number of convulsions. This is in keeping with the greater incidence of this complication late in the course of therapy and its progressive increase with continued therapy. In our experience, three convulsions per week tend to produce pronounced impairment of memory. We therefore prefer as a rule not to administer more than two treatments per week, although this schedule can be violated at times with impunity for one or two weeks. Shapiro and Freeman [10] and Friedman [11] stated that the induction of a period of confusion and amnesia has a definite therapeutic value. Because of the danger of irreversible residuals, we have preferred not to hazard this state.

Other predisposing factors to vulnerability of the memory faculty are additional drugs, generalized toxicity and cerebral organic changes, such as arteriosclerosis and chronic lethargic encephalitis. Yannet and Jannucci [12] produced greater cerebral damage with insulin when their animals received barbiturates in addition. In Platner's cases the Korsakoff syndrome developed from combined treatment with metrazol and insulin.

Significance of the Complication of Memory Impairment for the Future of Shock Therapy.—The question appears to be one of dosage. Severe damage to the nervous system with metrazol has been produced. Whether the usual course of treatment results in injury to the

10. Shapiro, H. D., and Freeman, W.: Shock Therapy (Insulin and Metrazol) in the Neuroses, M. Ann. District of Columbia **8**:65 (March) 1939.

11. Friedman, E.: Irritative Therapy of Schizophrenia, New York State J. Med. **37**:1813 (Nov. 1) 1937.

12. Yannet, H., and Jannucci, J. F.: Experimental Study of Pathogenesis of Cerebral Changes Following Prolonged Insulin Hypoglycemia, Arch. Neurol. & Psychiat. **42**:395 (Sept.) 1939.

nervous system cannot as yet be stated. Wittman [13] utilized batteries of psychologic tests, both before and after shock treatment, and failed to obtain evidence of such damage. The report of Davis and Sulzbach [14] on electroencephalographic evidence of injury to the nervous system in 1 case must be compared with that of a larger series studied with relation to the number of convulsions, particularly since Campbell [15] did not have the same experience. Likewise, data from histopathologic sources require reevaluation, since positive abnormalities were obtained in animals [16] and patients [17] receiving excessive medication. When the dose was small the adequacy of the controls in evaluating the damage is open to question. On the whole, recovered patients show no apparent permanent defects attributable to the treatment.

CONCLUSION

Four cases are reported in which moderately severe amnesia developed with metrazol treatment. Less marked changes are reported in 20 of 32 other cases. Usually the defect is minor and transient and may even escape detection if not sought for. Occasionally severe impairment, even the Korsakoff syndrome, may occur. Recovery is the rule.

The nature of the amnesia is that of the "organic" type and is the cumulative result of the residual postconvulsive memory impairments.

The memory abnormality is related to the number of metrazol convulsions. Two treatments a week for six to eight weeks is fraught with little or no disability. Arteriosclerosis and toxicity call for caution, and possibly fewer treatments. Sedative drugs may predispose to memory complication. The induction of a period of confusion has not been established as desirable, and may be harmful.

Similarity in the development of amnesia and therapeutic recovery suggests a common basic mechanism, related in part at least to the depressive or noxious action of metrazol convulsions on the brain.

The reversibility of the memory impairment in almost all patients removes this complication as a contraindication to metrazol therapy.

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13. Wittman, P.: Mental Efficiency Levels Before and After Shock Therapy, read at the meeting of the American Psychological Association, San Francisco, 1939.

14. Davis, P. A., and Sulzbach, W.: Changes in the Electroencephalogram During Metrazol Therapy, Arch. Neurol. & Psychiat. **43**:341 (Feb.) 1940.

15. Campbell, M., in discussion on Davis and Sulzbach.[14]

16. Liebert, E., and Weil, A.: Histopathologic Changes in the Brain Following Experimental Injections of Metrazol, Arch. Neurol. & Psychiat. **42**:690 (Oct.) 1939. Whitehead, R. W.; Neuburger, K. T.; Rutledge, E. K., and Silcott, W. L.: Pharmacologic and Pathologic Effects of Repeated Convulsant Doses of Metrazol, Am. J. M. Sc. **199**:816 (March) 1940.

17. Weil, A., and Liebert, E.: A Neuropathologic Study of Six Cases of Psychoses in Which Metrazol Was Used, Arch. Neurol. & Psychiat. **44**:1031 (Nov.) 1940.

TUMORS OF THE BRAIN IN AGED PERSONS

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Tumors of the brain have no respect for age; their type may vary with the various periods of life, but old age is no guarantee against their appearance. As the result of improved diagnostic methods, which include ophthalmoscopic, perimetric, roentgenographic, encephalographic, ventriculographic and, more recently, electroencephalographic examinations, physicians may have to modify the concept that tumors of the brain in aged persons are relatively rare. It is true that the cardinal signs of tumor of the brain are essentially the same in all periods of life, although in the aged patient they may be so modified that their significance escapes detection. Frequently, the natural penalties of advancing years will mask the early signs of a tumor and lead the physician to an incorrect evaluation of the symptoms unless he is cognizant of the frequency with which tumors of the brain occur in aged persons. Hastings [1] has aptly stated:

> The diagnosis of brain tumor may be a difficult matter at any age. But when tumor occurs at an age which also includes blood vessel catastrophes, the effects of syphilis on the brain, and the damages of senility, diagnosis may become very difficult indeed, and at times impossible.

If to this list of disorders are added the metastatic insults and an ill defined array of processes so common in the aged patient, the difficulties that are encountered in the diagnosis of tumor of the brain in this group of patients may be well appreciated.

For some time we have concerned ourselves with the problem of tumor of the brain in aged persons. In spite of our alertness to this situation we have found no uniform clinical procedures which would

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From the Section on Neurology (Dr. Moersch), the Section on Neurosurgery (Dr. Craig) and the Section on Neuropathology (Dr. Kernohan), of the Mayo Clinic.

1. Hastings, D. W.: Difficulties in Differential Diagnosis of Brain Tumors in Older Age Groups, J. Nerv. & Ment. Dis. **89**:44-51 (Jan.) 1939.

aid in the avoidance of the diagnostic pitfalls presented by tumors of the brain in patients of this age group. It is a frequent observation that tumors of the brain in the aged are overlooked or are permitted to pass with an incorrect diagnosis, such as cerebral arteriosclerosis, senility, cerebral softening, and the like, there appearing to be, generally speaking, a definite hesitancy on the part of the physician to render a diagnosis of tumor of the brain in cases of aged patients. If physicians are to sharpen their diagnostic acumen, it is imperative that the possibility of the presence of tumor of the brain in the aged be kept in mind. Then only can proper evaluation be made of the clinical symptoms presented by an aged patient in whom the usually recognized cardinal signs of tumor of the brain may be distorted as a result of mental and physical changes consequent to this period of life.

REVIEW OF MATERIAL

From the records of the Mayo Clinic for the past twenty years we have collected reports on 100 cases of verified tumors of the brain occurring among patients 60 years of age or more. This group of cases represents only a portion of the reports of tumors of the brain in aged persons that we have been privileged to examine. We have had to exclude those patients who were sent home after roentgen therapy for a supposed tumor of the brain, those patients for whom a decompression type of operation was performed after a diagnosis of tumor of the brain but concerning whom no positive diagnosis could be made at biopsy, those patients who refused an operation or who were advised against undergoing operation and those patients for whom palliative decompression was performed for a supposed primary or metastatic tumor of the brain. In addition, we have had to exclude a group of patients the nature of whose condition was uncertain, so that they had been sent home with a diagnosis of a vascular lesion of the brain, senility, organic dementia, or the like, but concerning whom the possibility of the presence of a tumor of the brain had to be entertained. A fair percentage of these patients did prove to have a tumor of the brain, as was demonstrated on their subsequent visits to the clinic or on the basis of follow-up information.

DURATION OF CLINICAL SYMPTOMS PRIOR TO EXAMINATION

The duration of the clinical symptoms prior to our examination of the patient was not always easy to determine. In the group of patients who had glioblastoma multiforme the histories covered a period of one month to three years. The average duration of symptoms was seven and four-tenths months. If the two longest histories are excluded as being inaccurate in the matter of the period of symptoms, the average duration was five and six-tenths months. In the group of 25 patients who had

meningiomas the history of symptoms ranged from three months to a possible twenty years, with an average duration of five years. In the group of 22 patients who had acoustic neuromas the duration of symptoms ranged from one to fifteen years. In several of the patients suffering from acoustic neuromas the exact time of onset of symptoms was difficult to determine, since the presence of deafness could not always be accepted as the first evidence of growth of a tumor. Thus, in 1 case in which the patient had a history of progressive symptoms extending

TABLE 1.—*Early Symptoms in One Hundred Cases of Tumor of the Brain*

Symptoms	Cases
Headaches	23
Mental symptoms	17
Tinnitus and deafness	16
Convulsions	11
Visual disturbance	8
Dizziness	6
Paralysis	4
Ataxia	3
Fatigue and weakness	3
Pain or paresthesia	4
Nausea and vomiting	2
Tumor growth on skull	2
Hiccup	1

TABLE 2.—*Chief Complaint at Time of Examination in One Hundred Cases of Tumor of the Brain*

Chief Complaint	Cases
Mental symptoms: dulness, confusion, stupor, etc.	18
Paralysis	16
Headache	15
Visual disturbance	13
Ataxia	13
Attacks of unconsciousness or convulsions	7
Dizziness or vertigo	7
Nausea and vomiting	5
Fatigue and weakness	3
Deafness (1 case), facial pain (1 case), hiccup (1 case)	3
Total	100

over fifteen years, deafness, which had followed otitis media, had preceded the progressive signs by ten years. As might be expected, patients suffering from malignant tumors of the brain had a relatively short history, but this shortness was not in itself of diagnostic importance when the duration of symptoms of patients in the group who had glioblastoma multiforme was considered.

SYMPTOMS ON EXAMINATION

Table 1 presents what is thought to have been the first symptom that the patient complained of as a result of the tumor of the brain. Table 2 presents the major complaint at the time of our examination

of the patient. Although headache was mentioned as a leading early symptom and was also common as a chief complaint, it is noteworthy that in only 15 cases was headache present (table 2). It should also be emphasized that mental symptoms of one type or another represented a prominent complaint, usually on the part of the family rather than on the part of the patient. Mental symptoms varied from mental dulness to stupor, with many interesting and bizarre clinical histories. In several instances the mental symptoms were looked on as resulting from senility or changes secondary to cerebral arteriosclerosis. Among staff members of the Section on Neurology of the Mayo Clinic an ill explained or bizarre progressive mental disturbance has come to be regarded as a possible organic dementia resulting from tumor of the brain and demanding careful investigation. Rapidly progressive mental changes occurred most frequently in the group of patients with glioblastoma multiforme. In the group with meningioma the mental changes, if present, were more insidious and suggested arteriosclerotic dementia or senility.

DIAGNOSTIC DIFFICULTIES

It is in the group of so-called vascular lesions that we encountered the most difficulty from the diagnostic standpoint. We have no accurate data relative to the correctness or incorrectness of our diagnosis in this group of cases. We do know that patients have been dismissed with a diagnosis of a vascular insult to the brain, organic dementia, or the like, only to have them return in a few weeks or months with definite signs of tumor of the brain or to learn of our mistake on the basis of follow-up information. Locke,[2] Stender,[3] Globus and Strauss,[4] Elsberg and Globus [5] and others have called attention to the problems involved in the differential diagnosis of tumors of the brain and cerebral vascular lesions. Stender and Elsberg and Globus have referred to the *Blitz*-like, or "acute," suddenness with which the symptoms of tumor of the brain may appear and to the difficulty in arriving at an accurate diagnosis, especially in an elderly person in the absence of papilledema.

That the diagnosis of tumor of the brain is no simple matter is illustrated by our experiences in the 100 cases of the series. Of this

2. Locke, C. E.: The Differential Diagnosis of Brain Tumor, Ann. Clin. Med. **5**:1097-1111 (June) 1927.

3. Stender, A.: Apoplektiformer Krankheitsbeginn bei Hirntumoren (Halbseitenlähmung), Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:123-168, 1938.

4. Globus, J. H., and Strauss, I.: Vascular Lesions and Tumors of the Brain: Difficulties in Differential Diagnosis; Report of Seven Cases with Necropsy Findings, Arch. Neurol. & Psychiat. **15**:568-587 (May) 1936.

5. Elsberg, C., and Globus, J. H.: Tumors of the Brain with Acute Onset and Rapidly Progressive Course: "Acute Brain Tumor," Arch. Neurol. & Psychiat. **21**:1044-1078 (May) 1929.

group, a correct diagnosis had been made in 60 cases prior to our examination. The remaining 40 cases are of interest because they represent the usual diagnostic difficulties encountered in cases of tumors of the brain in aged persons. Table 3 gives the diagnosis with which the patients came to the clinic. After careful study the 40 cases in which diagnosis was made incorrectly could be reclassified as follows: tumor of the brain, 13; possible tumor of the brain, 15; metastatic tumor of the brain, 3, and lesion of the brain of indeterminate type, 9. In the last 9 cases the patients died without a positive diagnosis or operation, and only at postmortem examination was it possible to make a correct diagnosis of tumor of the brain. Krabbe and Ellermann,[6] in discussing the diagnosis of tumors of the brain, stated that in 14 of a group of 18 cases of intracranial tumors a diagnosis of vascular disease of the

TABLE 3.—*Diagnosis on Admission in One Hundred Cases of Tumor of the Brain*

Diagnosis	Cases
Tumor of the brain	60
Cerebral vascular lesion	11
Cerebral arteriosclerosis	5
Senile dementia	3
Mental disease	2
Psychoneurosis	3
Convulsions	3
Syphilis of the nervous system	2
Disease of spinal cord	1
Encephalitis	1
Multiple sclerosis	1
Migraine	1
Cholecystitis	1
Vertigo	1
Indeterminate	5
Total	100

brain had been made. They, too, stressed the importance of considering the possibility of tumor of the brain in older patients, especially those who had a history of progressive hemiplegia.

In the diagnosis of tumor of the brain the acoustic neuroma did not present a difficult problem at the time of our examination, although many of the patients who had this condition had been treated previously for such conditions as vertigo, Ménière's disease and gastrointestinal disturbances. Meningioma presented a more difficult diagnosis, but thanks to roentgenographic examinations, more than one embarrassing mistake was avoided. In 6 cases of meningioma one of the major symptoms was a definite progressive mental change which at the patient's age might have been permitted to pass as a symptom of cerebral arteriosclerotic changes or senility.

6. Krabbe, K. H., and Ellermann, M.: Mistaken Diagnosis in Cases of Cerebral Tumors, Ugesk. f. læger **100**:925-930 (Aug. 18) 1938; abstracted, J. A. M. A. **111**:1706 (Oct. 29) 1938.

It is in the group of cases of glioblastoma that the greatest hazards in diagnosis were encountered. In 15 of our 35 cases the diagnosis was relatively easy. In 11 cases the question of the presence of a vascular lesion had to be given considerable thought, and in several instances the diagnosis was not determined until operation or postmortem examination. We have already referred to the reports by other observers regarding the diagnostic difficulties involved in the instances of so-called acute tumor of the brain and also in instances of progressive hemiplegia. In 13 patients who had glioblastoma mental symptoms were pronounced, and although they were not always the major complaint, they might readily have been interpreted as evidence of vascular encephalopathy or some form of organic dementia. In contradistinction to the mental changes observed in the group of patients suffering from meningioma, the mental symptoms in the group of patients suffering from glioblastoma were of shorter duration, although of the same general nature. It is again advisable to emphasize the fact that all too frequently the diagnosis of glioblastoma in patients 60 years of age or more is overlooked because of a short, shocklike clinical history, or at times of slowly progressive hemiplegia, and, finally, of progressive organic dementia. The mental and physical changes, or all signs, are interpreted as the result of vascular or degenerative changes in the brain attendant on the age of the patient, rather than as the result of a progressive intracranial tumor.

DIAGNOSTIC PROCEDURES EMPLOYED

Examination of Ocular Fundi.—In 96 of our 100 patients the ocular fundi were examined. In 32 patients papilledema was present, and in 8 patients there was evidence of atrophy of the optic nerves. Of these 32 patients, the results of perimetric examination were normal for 19. Eighty-eight patients had perimetric examination, 32 of whom had defects in the field of vision; 14 of the 32 patients had no evidence of papilledema. These facts are interesting, and also important, because they demonstrate the value of papilledema as a diagnostic sign, and they also emphasize the great care that must be exercised in diagnosis when the patients are not affected by papilledema. It would appear, on the basis of our study, that papilledema less frequently accompanies tumors of the brain in aged persons than it does in younger persons. The value of careful performance of perimetric tests cannot be minimized, for in the 32 instances mentioned previously the positive field defects were of localizing value and in 14 of these 32 cases there was no evidence of papilledema.

Examination of Spinal Fluid.—Seventeen of our patients underwent examination of the spinal fluid during preliminary study. At least 7 other patients underwent examination of the spinal fluid before coming

to the clinic. In our 17 cases the total protein value of the spinal fluid was increased, ranging from 50 to 220 mg. per hundred cubic centimeters. The reaction of the Nonne test was positive in all cases. Leukocytes ranged in number from 1 to 36 per cubic millimeter of spinal fluid. In 4 instances the spinal fluid was yellow. It is not recommended that examination of the cerebrospinal fluid be considered a routine procedure in instances of suspected tumor of the brain, but at times such examination is necessary to establish the correct diagnosis, as was true in several of our cases. Unless it is recognized that with tumors of the brain the total protein content of the spinal fluid may be increased and that there may be an increase in the cell count of the spinal fluid, observations made on the spinal fluid may lead to an incorrect diagnosis. In 97 cases there were flocculation tests of the blood for syphilis, with a positive reaction in 1 case. Results of examination of the spinal fluid for syphilis in this case were negative.

Roentgenographic Studies.—That roentgenographic examination of the skull plays a helpful role in the diagnosis of tumor of the brain should need no comment. In 30 of our 100 patients roentgenographic findings in the skull were helpful in making a correct diagnosis; this was true in 13 patients who had meningioma, 4 who had acoustic neuroma, 3 who had pituitary tumor, 2 who had carcinoma and 8 who had glioblastoma multiforme. The figure for the acoustic neuroma is low, but since we have become more diligent in obtaining good roentgenographic examinations of the porus acusticus we are obtaining a much higher percentage of positive roentgenographic findings.

Pneumographic and Electroencephalographic Studies.—Eighteen of our patients had pneumographic studies of the brain, 9 encephalograms and 9 ventriculograms being made. The majority of air studies were carried out on patients with glioblastoma multiforme. As nearly as we could determine, the pneumographic studies played no special role in the operative mortality. It so happened that no air studies were carried out in this series of cases without subsequent operation. We mention these facts because it has been our impression that elderly patients, especially, do not tolerate air studies well and that the procedure is hazardous unless it is followed immediately by an operation for decompression of the brain. In this series of cases only 4 patients had electroencephalographic examinations, but in each case the observations were of diagnostic value. It is premature to express a final opinion as to the value of electroencephalographic tests. It would appear from our observations on the electroencephalographic examination of patients in the age group under consideration that this new diagnostic adjunct will be of material help in diagnosis. This is especially true concerning those elderly patients

who present mental changes or have no evidence of papilledema but in whom one suspects tumor of the brain, which requires added diagnostic support before the more hazardous pneumographic procedure is recommended.

Readings in Blood Pressure.—Values for blood pressure in our cases ranged from 100 to 210 systolic and from 68 to 126 diastolic, expressed in millimeters of mercury. So far as we were able to determine, the values for blood pressure had no relationship to the type or situation of the lesion or to the operative mortality. The diagnostic importance of readings for blood pressure was not always easy to evaluate. The syndrome of malignant hypertension and papilledema is well recognized, but may escape recognition because of the presence of symptoms suggesting tumor of the brain. As has been pointed out by Grant [7] and also by Pepper,[8] malignant hypertension may simulate a tumor of the brain. Grant reported 5 cases of malignant hypertension in which a preliminary diagnosis of tumor of the brain had been made. This is an experience that is probably more common than is usually admitted. That the problem may be presented in exactly the reverse order is also to be borne in mind, since all too frequently a diagnosis of hypertensive encephalopathy is made in what later proves to be an instance of tumor of the brain.

INCIDENCE BY AGE AND BY SEX

Approximately 28 per cent of our total number of verified tumors of the brain occurred among patients 50 years of age or more. Of this total group, 8 per cent were found among patients 60 years of age or more. This figure represents a rapid decline in incidence, paralleling the increased age of the patients, but the decline is not so precipitous as that given by Bailey.[9] In Cushing and Eisenhardt's [10] series of 313 meningiomas, 19, or 6 per cent, occurred among patients 60 years of age or more. It seems reasonable to assume that our diagnosis may have been more accurate in the cases in which the lesions occurred in the age decade of 50 to 59 years and that the incidence of 8 per cent may be increased considerably with improvement in skill of diagnosis of tumor

7. Grant, F. C.: The Differential Diagnosis of Tumor of the Brain: The Importance of Considering Renal Hypertension with Choked Disk, Tr. Am. Neurol. A. **57**:300-311, 1931.

8. Pepper, O. H. P.: Malignant Hypertension Simulating Brain Tumor, Pennsylvania M. J. **35**:75-78 (Nov.) 1931.

9. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

10. Cushing, H., and Eisenhardt, L.: Meningiomas: Their Classification, Regional Behavior, Life History, and Surgical End Results, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

of the brain among patients 60 years of age or more. Badt,[11] in a report of 2,054 necropsies which included examination of the brain, found 57 cases in which tumor of the brain had not been diagnosed, but in a few cases the diagnosis had been surmised. In 33 of the cases a diagnosis of arteriosclerotic softening of the brain had been made. The patients in 22 of the 57 cases had experienced a "strokelike" onset of symptoms. Thirty-nine patients were more than 60, and 18 were more than 70 years of age. On the basis of our experience and that of others, we are repeatedly impressed with the need for the physician to be constantly on the alert for the possibility of tumor of the brain among patients in the advanced years of life, especially in the presence of acute cerebral symptoms or progressive cerebral changes.

In the 100 verified cases of tumor of the brain there were 61 men and 39 women. The ages of the patients ranged from 60 to 84. Ninety-one per cent of the tumors occurred among patients between the ages of 60 and 70; the remaining 9 per cent occurred among patients 70 years of age or more. The relation of the type of tumor of the brain to the average age of the patients at the time of examination at the clinic was as follows: pituitary tumor, 62 years; acoustic neuroma, 62 years; carcinoma, 63.5 years; glioblastoma multiforme (spongioblastoma multiforme), 64 years, and meningioma, 64 years.

ANATOMIC DISTRIBUTION AND TYPES OF TUMORS

Sixty-seven of the tumors were found in the cerebrum and 27 in the posterior fossa of the skull; in 6 cases the tumors were multiple, involving the cerebrum in 4 instances and both the cerebrum and the cerebellum in 2. Classification as to the type of tumor gave 35 glioblastomas multiforme, 25 meningiomas, 22 acoustic neuromas, 3 pituitary tumors, 8 carcinomas, 2 sarcomas, 1 hemangioblastoma, 1 astrocytoma, 1 oligodendroglioma, 1 craniopharyngioma and 1 melanoma. In our series of cases we found no glioblastomas in the cerebellum. There were 1 oligodendroglioma and 1 hemangioblastoma in the cerebellum and 1 astrocytoma in the right temporal lobe. A single meningioma was found in the posterior fossa, and that was a meningioma of the cerebellopontile angle. A possible deduction, based on the situation of the tumors, would be that meningiomas occur rarely in the posterior fossa and that when they are present they are most likely to be situated in the cerebellopontile angle. It may also be stated that glioblastoma in the age group under consideration occurred rarely in the cerebellum. It is surprising that so few of the slow-growing gliomas are represented in our series of

11. Badt, B.: Bericht über 57 nichtdiagnostizierte Hirntumoren, zugleich ein Beitrag zur Symptomatologie der Hirntumoren im Senium, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:610-656, 1932.

cases. A follow-up study of those patients who were permitted to return home and for whom the diagnosis of tumor was not verified might materially alter our figures.

RESULTS OF OPERATION

Eighty-six of the 100 patients underwent operation for tumor of the brain, and the diagnosis was verified by either biopsy of the tumor or postmortem study. Fourteen patients died without undergoing operation; postmortem studies made in these cases verified the diagnosis of tumor of the brain. Of the 86 patients operated on for tumor of the brain, 37, or 43 per cent, succumbed during their immediate hospitalization, from the results of the operation, postoperative complications or the effects of the rapidly growing tumor. It seems proper to emphasize the fact that many of these elderly patients presented a grave operative risk and operation was undertaken either in the hope of saving what vision remained or, in some instances, of saving life. In our experience elderly patients, especially those who did not have papilledema or other evidence of marked increase of intracranial pressure (which pressure usually proved to be the result of glioblastoma multiforme), presented the most serious operative risk. Patients who had meningiomas and acoustic neuromas also had a higher operative mortality than a corresponding group of younger persons who had similar forms of tumor. The excellent operative results obtained for the latter group of patients compensated in a measure for the increased operative mortality presented by our entire series of aged patients suffering from tumors of the brain. The duration of life following operation could be determined in less than half the cases, because no complete follow-up study in the remaining cases was possible. In 11 cases of glioblastoma multiforme in which the patients were followed the average length of life subsequent to operation was four months. In the 12 cases of meningioma the postoperative duration of life of the patients was two and a half years, and in 9 cases of acoustic neuroma the postoperative duration of life of the patients was three and a half years. We are aware that our figures on the length of life following operation are accurate only for the small group of patients whom we were privileged to follow. We know that in cases of meningioma and of acoustic neuroma the postoperative span of life may be much longer; indeed, a survival of fifteen to twenty years is not unusual, but in our group of patients of advanced years no such long periods of life were noted. It is possible that some of the patients whom we were unable to follow may have survived for many years. An important factor to bear in mind regarding postoperative longevity is the fact that in this age group the natural expectancy of life is relatively short, and some of the patients undoubtedly died of causes other than those resulting from tumor of the brain.

SUMMARY AND CONCLUSIONS

From our review it appears that the incidence of tumor of the brain in the aged is more common than is usually appreciated. Glioblastoma multiforme, meningioma and acoustic neuroma, in the order named, made up 82 per cent of the tumors in our series of cases. The cerebrum was the most common site of development of tumor, tumors in this region constituting 69 per cent in our cases. In the posterior fossa the cerebellopontile angle was the usual site of the neoplasm, which usually was an acoustic neuroma. As a result of the penalities of advancing years, the symptoms and signs of tumor of the brain were exceedingly variable and at times resulted in difficult diagnostic problems. The presence of papilledema or defects in the fields of vision was an important diagnostic aid; however, their absence could not be accepted as proof of the absence of a tumor of the brain. Only 32 of 96 patients examined had papilledema. It is at present probably too early to draw conclusions regarding the value of the electroencephalogram as a diagnostic procedure, but it may be hoped that this divining tool may be of considerable diagnostic aid in cases of elderly persons suspected of having a tumor of the brain. The operative mortality accompanying tumor of the brain, although it is higher among patients of advanced years than it is in a group of younger persons, probably could be justified on the grounds that operation might save a life which otherwise the tumor would end. There is always the possibility of uncovering a removable tumor of the brain in spite of a patient's relatively short clinical history, thus justifying the increased surgical risk.

MECHANISM OF DISPLACEMENT OF THE VENTRICULAR SYSTEM IN CHILDREN WITH ATROPHIC LESIONS

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The fact that the midline structures and the contralateral ventricle sometimes move toward the atrophic side in patients with asymmetric lesions of the brain is universally recognized. It is also recognized that such movement does not always take place. In the rather confusing literature on the subject there are references to meningeal adhesions, to shrinkage of cerebral tissue and to asymmetric growth as factors of importance.

In 1938 Casamajor and Laidlaw [1] stressed the role of unequal growth. In the same year one of us (B. C.) [2] suggested that, in children, asymmetric growth is of outstanding importance. In 1939 Robertson and Childe [3] showed that adhesions could not explain the dislocation in many cases.

In this paper the results of a study of encephalograms of children are reported. All cases in the hospital files in which asymmetry was present were reviewed with particular reference to the mechanism which produces displacement. The only point which is discussed here is the lateral movement of the midline structures and of the contralateral ventricle in cases with predominantly unilateral atrophy. It is taken for granted that any degree of dilatation or distortion of the ventricle on the side of the lesion can be accounted for by adhesions or atrophy. The question

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1. Casamajor, L., and Laidlaw, R. W.: Convulsive States with Evidence of Brain Hemiatrophy, Am. J. Psychiat. **96**:165, 1939.

2. Crothers, B.: The Influence of Age on Ventricular Displacement in the Hemiplegias of Childhood, Am. J. Dis. Child. **50**:45 (July) 1938.

3. Robertson, J. S., and Childe, A. E.: Relation of Ventricular Asymmetry to Contracting Intracranial Lesions, Arch. Neurol. & Psychiat. **43**:80 (Jan.) 1940.

is whether the midline structures and the contralateral ventricle move in response to pressure or to traction or to combinations of the two.

In the hospitals from which this report is made the encephalographic procedure is regarded as a severe but entirely reasonable method of study. It is carried out, under careful supervision, by members of the pediatric service, as well as in the neurologic and neurosurgical services. Most of the children with mental defect or epilepsy who are selected for ward study are subjected to this procedure. In addition, during the last few years most cases of recent hemiplegia have been investigated by this method. Naturally, therefore, a very large number of cases in which there were no expanding lesions has been collected.

The review of the encephalographic material revealed 487 cases in which asymmetry or lateral dislocation of the ventricles was seen. The total number of cases reviewed was 1,700. These encephalograms were first reviewed without reference to clinical records. It was felt that it was fair to exclude certain films on the ground of inadequate filling or inconclusive evidence for some other reason. In addition, it was felt that slight asymmetries of the posterior horns alone rarely caused dislocation of the midline structures, so that cases in which no displacement was seen were excluded. Moreover, cases in which expanding lesions, such as subdural hematomas, abscesses and tumors, appeared to be present were omitted. In addition, several cases in which extensive operations on the skull had been performed before encephalographic examination were left out. The clinical records were then consulted, and a few more cases were excluded. The remainder of 173 cases appeared to represent the material in which "atrophic" lesions could be assumed.

The most relevant view was the anteroposterior, showing, in good films, the bodies of the lateral ventricles and the third ventricle. Most of our cases were taken with the child flat on its back with the film beneath the occiput and the tube 30 inches (76 cm.) away. Most of the encephalograms were taken with the subject under general anesthesia, induced chiefly with avertin with amylene hydrate and ether, and the air was usually introduced in the lumbar region.

The preliminary review of records and films resulted in a few impressions, but it was impossible to work out any system of records or measurements which would be useful without going over and over the films. The only practicable method seemed to be the assembling of a mass of small photographs and the subjecting of these to appraisal from various points of view. Admittedly, much detail is missed, but the gross displacements are easily seen.

Two large groups were easily identified. In one, both ventricles were large and rounded. Regardless of asymmetry, relatively little dislocation of the midline structures was seen.

A second group consisted of cases in which one ventricle was sharply defined and the other rounded and large. In certain cases in this group there was extreme dislocation, and it was not evident that there was any relation between the degree of enlargement on the atrophic side and the degree of displacement.

Next, an attempt was made to find valid encephalographic criteria by which adhesions could be recognized. We completely failed to establish such criteria, and therefore have no evidence as to the importance of adhesions.

We next divided the cases according to age at onset. It at once became clear that among the cases in which the lesion antedated or was coincident with birth a considerable number of dislocations occurred. Moreover, the cases of extreme dislocation were largely in this group.

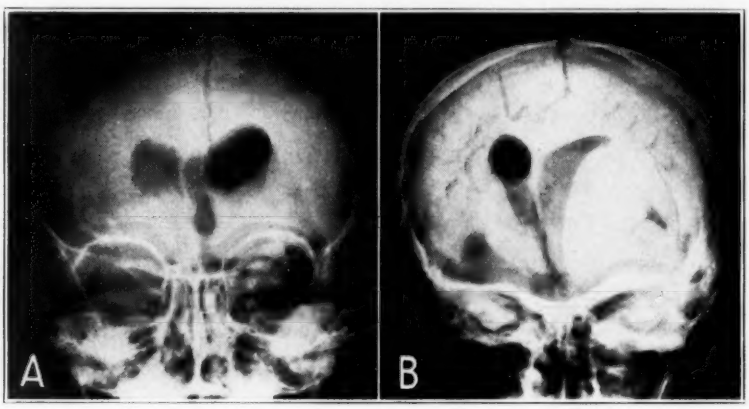

Fig. 1 (group A: prenatal cerebral defect).—*A* (case 1): The child in this case had a bilateral congenital anomaly of the eye. An encephalogram, taken at the age of 3 years and 5 months, shows asymmetry, but both ventricles are large and rounded. There is no dislocation.

B (case 2): The child in this case had congenital absence of one eye. An encephalogram, taken at the age of 3 years and 3 months, shows relatively little difference in size of the ventricles, but one ventricle is comparatively normal in contour, and the movement of the whole ventricular system toward the less normal side is striking.

On the other hand, in many cases no dislocation was apparent in spite of gross asymmetry. Here, again, the most striking point was the almost invariable presence of a relatively normal ventricle on the side opposite the atrophic lesion in the cases of serious dislocation.

In the group of children with histories suggesting, or proving, postnatal onset of symptoms we found the same general situation. Almost without exception, gross dislocations occurred in cases in which the ventricle on one side was normal in contour. The age at onset was

Fig. 2 (case 3, group B: premature babies).—A boy admitted to the Infants' Hospital was said to have been born three months before term. His weight was 2 pounds and 7 ounces (1,105 Gm.). Hemiparesis was first noticed when he began to walk, at the age of 2 years, but there was no history of accident or illness in the meantime. On encephalographic examination, at the age of 4 years and 10 months, gross atrophy in the posterior part of the left hemisphere was seen. As far as size is concerned, the asymmetry of the anterior parts of the ventricular system is slight, but displacement is evident.

Fig. 3 (case 4, group B: premature babies).—A girl, born two months before term, weighed 3 pounds (1,306 Gm.) at birth and was cyanotic. She had convulsions later. Two encephalograms, one taken at 11 months and the second at 6 years of age, show asymmetry. Both ventricles are large, and no displacement has occurred.

important, since the children whose disturbance dated from infancy showed more displacement than those whose lesions occurred after 2 years of age.

Fig. 4 (case 5, group C: birth injury at term).—The boy in this case was born by breech extraction, possibly a few weeks prematurely. An encephalogram, taken at the age of 7 years, shows practically complete destruction of one hemisphere with moderate enlargement, but no gross distortion, of the opposite ventricle. There is slight displacement.

Fig. 5 (case 6, group C: birth injury at term).—Hemiplegia was noted at the age of 6 to 8 months, with no previous illness. An encephalogram, taken at the age of 2½ years, shows striking displacement and moderate asymmetry.

The attempt to collect reliable information about the influence of lapse of time on displacement was not particularly conclusive, but we felt that the age period had much to do with displacement, and consideration of

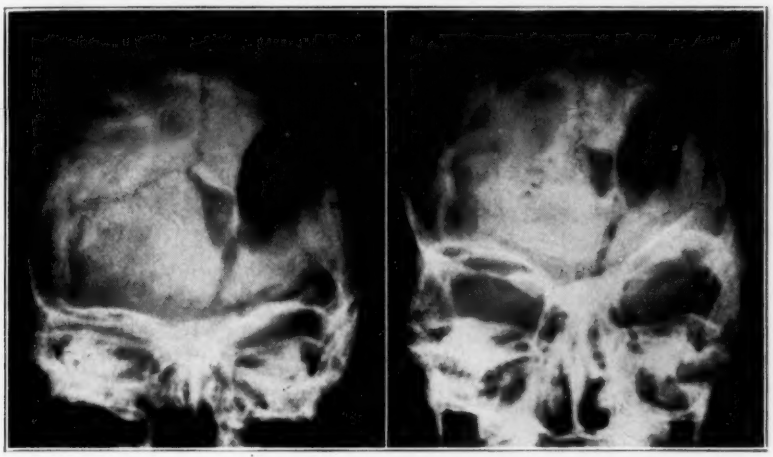

Fig. 6 (case 7, group C: birth injury at term).—The child in this case was delivered at full term by instruments, after five hours of labor. Multiple hemorrhages, occurring soon after birth, were treated by transfusions. The patient never used the right hand and arm well. He had many convulsions on one side. When he began to walk, at the age of 19 months, definite hemiparesis was noted, and has persisted. Encephalograms, taken at the age of 2 years and 10 months and again at 5 years and 11 months, both show great dislocation and asymmetry, with a normal right ventricle.

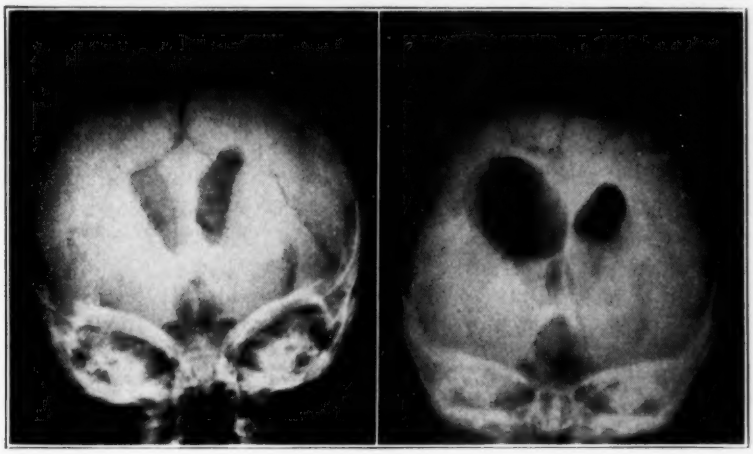

Fig. 7 (case 8, group C: birth injury at term).—The boy in this case was delivered without difficulty except that birth was precipitate. On the fourth day cyanosis, high fever and twitching of the right side of the body appeared. Hemiparesis was noted at the age of 2 months. The first encephalogram, taken at the age of 6 months, shows moderate asymmetry without displacement. The second encephalogram, at the age of 1 year and 5 months, shows increased asymmetry but no displacement.

figures on growth of the brain gave support to our impression that time was important chiefly because it provided opportunity for asymmetric growth.

The grouping of cases according to the presumed nature of the pathologic process brought out one or two points of interest. First, we could see no great difference between gross trauma with fracture of the skull and other lesions in which the meninges were presumably not damaged. Second, certain encephalopathies, such as that due to lead, never seemed to produce gross displacement, in spite of the fact that extreme asymmetries were common. The suggestion is made that the serious general edema which is present in cases of severe lead encephalopathy almost always causes bilateral interference with growth. Another point is that practically all lead poisoning in our series occurred in chil-

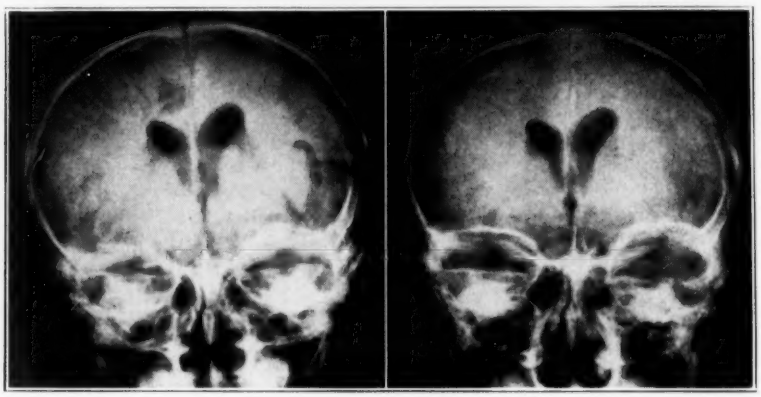

Fig. 8 (case 9, group C: birth injury at term).—Probable injury at birth. An encephalogram, taken at the age of 5 years, shows asymmetry without dislocation. Both ventricles are rounded. No appreciable change was noted when encephalographic examination was performed again, at the age of 10 years.

dren after the teeth had developed enough to make an effective attack on paint, so that much growth of brain mass had already occurred before the onset of encephalopathy.

This survey revealed a few disconcerting films. For instance, we found 3 cases of bilateral enlargement in which slight displacement was toward the side of the smaller ventricle. Occasionally definite dislocation toward the more damaged side occurred when both ventricles were large. However, the general proposition that asymmetric growth of brain mass is the fundamental mechanism of displacement in children with atrophic lesions still seemed defensible.

Attempts at statistical arrangement of this evidence failed completely. The variation in size of skull, the gross asymmetries of the skull and

the different types of defect of brain tissue made measurements confusing. Obviously, the most valid type of investigation would be based on serial encephalograms in each of a series of cases. We have little evidence of that sort available.

The only method of presentation that occurred to us was that of sampling. The chosen films are obviously the striking ones, but they are representative. The order in which they are shown is, of course, based on our conclusion that asymmetric growth is the fundamental mechanism which produces displacement.

SUMMARY

The encephalographic procedure has been carried out on approximately 1,700 children at the Children's and the Infants' Hospital. With occasional exceptions the children were under 12 years of age. In 172 cases, or approximately 10 per cent of the total, there was asymmetry of the ventricular system which appeared to be due to so-called atrophy. Cases in which expanding lesions appeared to be present were excluded in this review.

Any statistics have to be taken rather lightly, since it is impossible to include all relevant factors without confusion. Furthermore, there

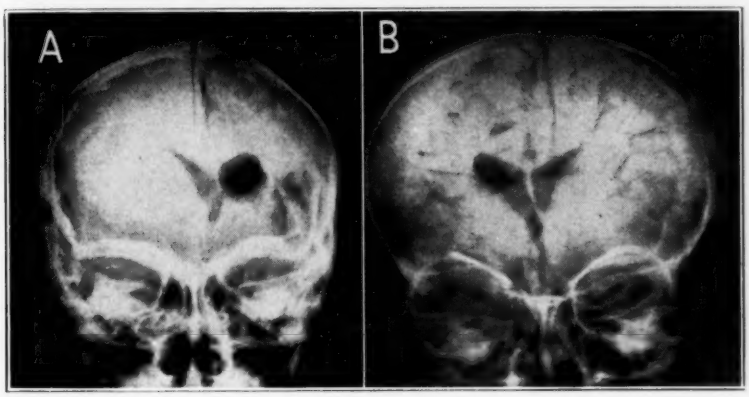

Fig. 9 (group D: postnatal encephalopathies).—*A* (case 10): The girl in this case came to the hospital at the age of 9 years and 3 months. There was a history, for what it was worth, that in early infancy the baby was dropped and thereon hemiplegia developed. The informant was the stepmother, who relied entirely on hearsay. The encephalogram reveals extreme displacement, with the ventricle opposite the lesion small and sharp.

B (case 11): At 18 months of age the child fell with a lollypop on a stick in her mouth. There was some pharyngeal bleeding, followed by fever after a few days. After this illness hemiparesis developed, which persisted until the time the encephalogram was taken, at the age of 3½ years. Moderate asymmetry with marked dislocation is shown.

were many films in which exact judgment was difficult on account of cranial asymmetry. In some cases deep subarachnoid spaces were seen; in others gross defects, usually classified as porencephalic cysts, were evident. For what they are worth, however, the statistics are as follows:

Of the 172 cases in which asymmetry was shown, definite displacement of the midline structures appeared in 68. In 65 cases this displacement was toward the more atrophic side; in 3 it was toward the less atrophic side. Of cases in which both ventricles were round and large, displacement occurred in 19 and no displacement in 74. On the other hand, of cases in which one ventricle showed approximately normal outlines, displacement occurred in 49 and no displacement in 30.

Obviously, the term atrophy, which is used in this paper, is open to objection unless it is defined. In many of the cases in this study we

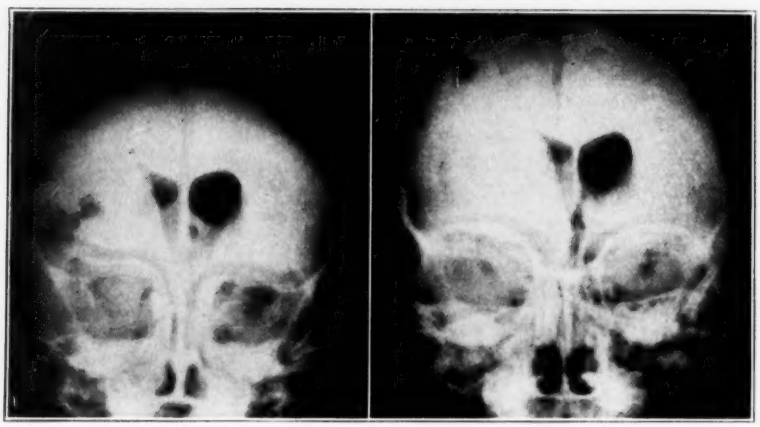

Fig. 10 (case 12, group D: postnatal encephalopathies).—The girl was brought into the hospital with convulsions and hemiplegia immediately after an automobile accident, at the age of 10 months. Lumbar puncture showed no blood; the spinal fluid pressure was low and the fontanel level. The next day infection of abrasions was evident, and no further investigation was made until shortly before discharge from the surgical service, six weeks later, at the age of 1 year. An encephalogram taken at that time showed asymmetry without dislocation. A moderate amount of subdural blood was evacuated through burr holes.

Three years later a second encephalogram showed an orderly movement toward the affected side. Puncture through the old burr holes demonstrated no subdural fluid.

This injury occurred after the very rapid period of growth. There was no evidence of bilateral injury, and the dislocation appears to be due to steady, slow growth.

have no evidence that any progressive deterioration was present. In some of the cases we have evidence, on repeated encephalographic examination, that resumption of growth occurred. All that we mean to imply by use of the term atrophy is that the process is a relatively inactive

one, leading to diminution of the expected bulk of all or part of the cerebral hemispheres. The term has no implications as to etiologic factors or prognosis.

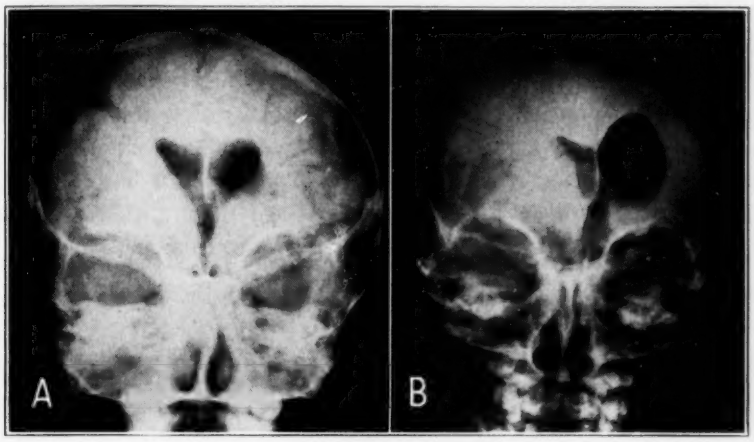

Fig. 11 (group D: postnatal encephalopathies).—*A* (case 13): At 21 months of age the girl fell from the second story porch and suffered a widespread comminuted fracture of the left side of the skull. The encephalogram, taken at 8½ years of age, shows almost no displacement. At the operation which followed widespread, firm adhesions were observed which bound the brain to the skull, and even to subcutaneous tissues.

B (case 14): Convulsions with onset during whooping cough, at the age of 13 months. An encephalogram, taken at 2 years and 8 months, shows gross asymmetry and dislocation.

Fig. 12 (case 15, group D: postnatal encephalopathies).—Known lead poisoning occurring in a normally developed boy, at the age of 18 months. The encephalogram, taken at the age of 3½ years, shows extreme asymmetry without important dislocation.

Lateral dislocation of the midline structures and of the contralateral ventricle toward a unilateral atrophic lesion was not a constant finding. In fact, in children with asymmetric ventricles serious displacement of the midline structures was relatively uncommon.

The mechanism by which the midline structures are displaced is the only point discussed. For the sake of uniformity the position of the ventricular bodies and midline structures was studied in anteroposterior films. The arrangement of the dural septums makes any lateral displacement of the occipital portion of the system almost impossible, and our material does not lend itself to study of the anterior horns.

The falx, even in infancy, appears to be a structure of strength and importance, and it is not easy to believe that it can be dislocated except

Fig. 13 (case 16, group D: postnatal encephalopathies).—The girl in this case was apparently normal until she had convulsions on one side, at the age of 3½ years. The encephalogram taken at that time shows diffuse, slightly asymmetric involvement of the whole brain. A second encephalogram, at the age of 5½ years, shows what we interpret as recovery on one side with progressive atrophy on the other. In this case, as in a few others, the falx is almost in the midline, while the third ventricle has moved over toward the atrophic side.

by force, unless the general intracranial pressure suddenly falls in very early infancy. It is then conceivable that an actual reduction in size of the skull might leave it free to move. This situation is almost certainly sometimes present in newborn infants, but must be transient and unusual. Certainly, after the skull becomes reasonably rigid it can be assumed that the falx will hold its medial portion unless force is applied to it. It is well known that the falx, and with it the other midline structures, as well as the cranial vault itself, will yield to pressure. This pressure may be from an expanding lesion, or it may be from unopposed growth of one hemisphere. Naturally, the factor of growth is particularly important in childhood.

The other force which can displace relatively rigid tissues is traction. Obviously, it is necessary to provide adequate anchorages and a line, of proper tensile strength, between them, before effective force can be exerted. It is well known that all the spaces between cortex and skull can be abolished by adhesions. An outer anchorage, therefore, is often provided. In order to pull effectively on the falx, and on the mass of the contralateral hemisphere, it would appear to be necessary to obliterate subarachnoid and subdural spaces on each side of the falx. With the anchorages in order it is then necessary to find a line along which effective traction can be exerted. In each of our series of pictures the ventricle, often greatly enlarged, lies directly across some part of the area between the skull and the falx and the other midline structures. No

Fig. 14 (case 17, group E: disconcerting films).—At the age of 1 year the boy in this case had an acute febrile illness, with convulsions and coma. An encephalogram, taken at the age of 3 years and 3 months, shows obvious enlargement of the whole ventricular system with dislocation toward the more enlarged ventricle. In this case further investigation was refused by the family, and it seems possible that a walled-off accumulation of fluid may explain the failure of the dislocation to follow the rules suggested in this paper. We have seen the same situation in a second case in which complete investigation was not carried out. Except for these 2 cases, no convincing dislocation toward the larger ventricle was seen.

evidence for the existence of traction by adhesions as a factor in displacing the midline structures toward an atrophic lesion is presented here, because we could not identify adhesions in encephalograms.

In our material, asymmetry of the ventricular outlines was the only constant finding, which of course simply represents our selection of cases. Usually one ventricle was larger than the other; sometimes the outlines were different on the two sides, and now and then the only unusual finding was lateral displacement.

As we compared the ventricular outlines in the cases in which dislocation occurred and those in which none was found, it seemed clear that the size and contour of the larger ventricle were unimportant. The major difference between the two groups was found on the relatively intact side. Unless the ventricle on this side was of approximately normal contour and of moderate size, no important displacement seemed to occur. It seemed clear, also, that displacements did not occur unless the brain on the more normal side reached the inner surface of the skull. We feel justified in assuming that these observations represent growth of one side.

The figures on growth of brain mass on which we rely are those used in the pathologic department of the Children's and the Infants' Hospital. The weights of premature brains are given with many reser-

Fig. 15 (case 18, group E: disconcerting films).—Child with apparently clear trauma at birth after breech extraction. The smaller ventricle is still large, and there is marked displacement toward the more atrophic side. There is no evidence of accumulation of fluid, and no explanation is offered in this case.

vations, since weight and body length, as well as brain weight, vary enormously in premature infants. However, it is common to find weights below 200 Gm. for babies at the end of seven calendar months of gestation. At term the figure is 335 Gm. This is doubled at 6 months, tripled at 18 months and not quadrupled until 12 years of age. Obviously, our material is too limited to justify definite conclusions on the effect of injury at each period, but in general we believe that any injury in infancy leads to far greater displacement than do comparable injuries in later childhood. Most of our extreme dislocations occurred in children who suffered from strictly unilateral injury before the beginning of the third year.

The attempt to deal with the material on an etiologic basis was not particularly profitable. The only thing that seemed clear was that diffuse

encephalopathies, such as those due to lead and alcohol, although they frequently produced hemiplegia and unequal destruction of brain tissue, did not cause displacement. Possibly the fact that all our children with this type of encephalopathy were older infants or young children at the time of onset had some bearing, but we are inclined to emphasize the widespread, though uneven, destruction.

It appears from our evidence that reliance on asymmetry of growth for explanation of lateral dislocation toward an atrophic lesion leads to less frustration than any other hypothesis.

There are various ways of testing the hypothesis set up here. Serial encephalograms, of which we have few, offer one method. Repetition of encephalographic examination after extensive operations, with at least temporary release of adhesions, offers another. Encephalographic study after resection of considerable masses of supratentorial tissue at various ages would provide more evidence.

Naturally, crucial evidence of this sort is not easily collected, and we draw conclusions about growth in most of our cases on the basis of single observations. We recognize the tentative nature of such conclusions.

With this material as a basis for argument and with full recognition of the limitations of the approach, we believe that certain conclusions are justified.

The acceptance of asymmetric growth as the fundamental mechanism of displacement of the ventricular system in children with atrophic cerebral lesions involves a certain amount of readjustment of ideas toward this phenomenon. First, if the hypothesis is correct, displacement is a favorable sign, in young children at least, since it indicates normal power of growth of one hemisphere. Second, attempts to modify displacement of the midline structures by operative attack on the damaged side are illogical. Finally, the skeletal changes, such as thickening and flattening of the calvarium and enlargement of the sinuses on the atrophic side, can be logically explained, since the orderly control of bone growth by orderly increase of brain mass is not in operation on the damaged side.

CONCLUSIONS

Consideration of our material, of which samples have been presented here, leads us to the following conclusions:

1. In children with asymmetric ventricles the midline structures and the contralateral ventricle move toward the atrophic side as soon as the sound hemisphere needs space.

2. If both hemispheres are damaged and fail to grow important dislocation rarely takes place, regardless of asymmetry.

3. Since growth is most rapid in the prenatal period and in the early months of independent life, the finding of maximal dislocation when the injury occurs in early life is easily explained.

4. If dislocation is the result of growth, failure of dislocation in the presence of gross asymmetry of the ventricles, in early childhood at least, may be a sign of bilateral failure of cerebral development.

5. No evidence was found to support the hypothesis that traction can pull the midline structures and the contralateral ventricle toward an atrophic lesion.

6. The mechanism of displacement may be the same, whether the pressure comes from unresisted thrust from a growing hemisphere or from an expanding lesion.

AN AMERICAN FAMILY WITH PELIZAEUS-MERZBACHER DISEASE

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In 1933, Löwenberg and Hill [1] described a degenerative disease of the white matter of the brain which they called "diffuse sclerosis with preserved myelin islands." The authors pointed out that this type of demyelination was identical with that seen by Merzbacher [2] and by Spielmeyer and Liebers [3] in a hereditary disease which occurred in four generations of one family. In spite of the close morphologic similarity, Löwenberg and Hill found no evidence of hereditary transmission at that time and concluded that the disease was sporadic, similar to that in the cases observed by Bodechtel [4] and by Bielschowsky and Henneberg.[5] The latter conclusion proved to be erroneous, since recently we have obtained sufficient evidence to show that this disease occurred in at least 5 cases and in two generations of the same family.

REPORT ON CASES OCCURRING IN ONE FAMILY

In July 1939 one of us (C. D. C.) examined Mrs. Edith S. C., aged 56. The patient had been in ill health for the past eighteen to twenty years. Her symptoms began with a tremor of the head, which gradually became more pronounced, involving as the disease progressed the jaw and the hands. During the last five to six years increasing difficulty in walking developed. In the last stages of the disease the patient complained of pain in the neck and back. Approximately six months prior to death the tremor of the arms and difficulty in walking increased to such an extent that she became unable to feed herself and was confined to bed. In June 1939, three months before her death, she suffered an attack which the relatives described as "a stroke" and which was said to have affected the right side of the body and was associated with difficulty in swallowing and disturbances in speech and vision. These symptoms disappeared within a few days. In July

From the Departments of Neurology (Prof. C. D. Camp) and Psychiatry (Prof. R. W. Waggoner), University of Michigan Medical School.

1. Löwenberg, K., and Hill, T. S.: Diffuse Sclerosis with Preserved Myelin Islands, Arch. Neurol. & Psychiat. **29**:1232 (June) 1933.

2. Merzbacher, L.: Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:1, 1910.

3. Liebers, M.: Ztschr. f. d. ges. Neurol. u. Psychiat. **115**:487, 1928.

4. Bodechtel, G.: Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:487, 1929.

5. Bielschowsky, M., and Henneberg, R.: J. f. Psychol. u. Neurol. **36**:131, 1928.

1939, four weeks before her death, neurologic examination by one of us (C. D. C.) revealed the following condition: The patient was unable to rise or stand without support. There was pronounced intention tremor of the head and jaw, which increased markedly when the patient was trying to sit up. Speech was impeded by the tremor of the jaw, but was understandable. There was a decided tremor of the hands on extension and in the finger to nose test. The umbilical reflexes were absent; the knee and achilles jerks were exaggerated, but there was no Babinski phenomenon. The pupils were equal and reacted to light and in accommodation; the ocular movements and the fundi were normal. There was no atrophy of the muscles, deformity of the limbs or paralysis. No objective sensory disturbances were elicited. Physical examination revealed only the presence of a harsh, short systolic murmur.

According to information obtained from relatives, the patient had always been conscious of her condition and became very irritable and seclusive. As the disease progressed the mental faculties declined. In the last few years she had become incompetent in handling money and unable to run her household, her judgment become poor and she had grown very forgetful and was at times confused. During

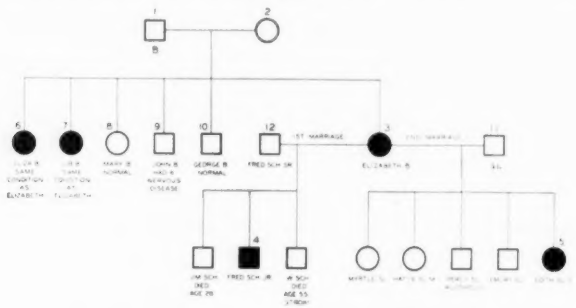

Chart 1.—American family B with Pelizaeus-Merbacher disease.

the last six months mild paranoid trends had appeared and she accused her husband of infidelity. Her speech became worse, and she repeated words and sentences over and over again.

In summary, the clinical picture was characterized by progressively increasing tremor of the head, jaw and extremities; attacks of a peculiar character in which the patient would become helpless but from which she would apparently recover in a few days; slight neurologic abnormalities, such as absence of the umbilical and exaggeration of the knee and achilles reflexes, and, mentally, mild depressive states, paranoid trends and increasing deterioration. All these findings suggested a diffuse degenerative disease of the white matter.

Genealogic investigation disclosed 4 other cases of the same nervous disorder in two generations of the family of Mrs. Edith S. C. (*5*, chart 1). One of these was her half-brother, Fred S. Jr. (*4*), whose brain was described in the article of Löwenberg and Hill previously referred to and whose case was grouped by them pathoanatomically with the 2 cases of heredofamilial disease of Merzbacher and Spielmeyer and Liebers.

Further genealogic investigation of this family elicited little information concerning the maternal grandfather (*1*). He died of tuberculosis at the age of 64, and there was no evidence that he had a nervous disorder. There was no infor-

mation concerning his family. The maternal grandmother (*2*) lived in England, and no records concerning her and her family were available. By this union there were 6 children, 4 females and 2 males. Of these 6 siblings, 3 definitely suffered from the same disorder: Elizabeth B. (*3*), Eliza B. (*6*) and Lib B. (*7*). Elizabeth B. (*3*), who was the mother of our patients, Fred S. Jr. (*4*) and Edith S. C. (*5*), suffered from a nervous disorder which according to statements of all relatives was "exactly like that of her two afflicted children" (*4* and *5*): "She shook all over her body," suffered "strokes," which, however, paralyzed her only for a few days and deteriorated mentally in the advanced period of her disease. She died in the middle of the sixth decade of life, i. e., at the same age as her afflicted children.

Eliza B. (*6*) suffered from "shaking palsy" closely resembling that of her sister Elizabeth B. (*3*) and died at the age of 60, after an illness of many years. Another sister, Lib B. (*7*), was described by relatives as "a nervous wreck." Her symptoms greatly resembled those of her two sisters. She also "shook all over" and was mentally deranged. Her age at the time of her death is not known to us. A fourth sister, Mary (*8*), is still living, apparently in good health. Of the 2 brothers, John (*9*) had a nervous disease which caused his death, but nothing is known of the nature of the disorder. The other brother, George (*10*), is still living and is in good health; his age is unknown to us.

Elizabeth B. (*3*) was married twice, to normal and healthy men. By the first marriage, to Fred S. Sr. (*12*), there were 3 male children. Of these, Fred S. Jr. (*4*) was the patient of Löwenberg and Hill. By the second marriage, to Cl. (*11*), there were 5 children, 3 boys and 2 girls. Of these, so far as is known, only 1, Mrs. Edith S. C. (*5*), suffered from the disorder under consideration. She had 1 son, who, at the age of 28, is married and the father of an infant son. He and his family are healthy.

The children of Eliza B. (*6*) and Lib B. (*7*) are said to be normal.

COMMENT

So far as available information permits, it can be stated that the transmission of the disease follows a dominant trend in both sexes, being transmitted from the mother to the children. This is particularly evident in the case of Mrs. Elizabeth B. (*3*), who had 1 afflicted male child by the first husband and 1 afflicted female child by the second. Although there is no sex linkage, females were predominantly affected (4:1). The third generation, so far as known, remained free of this disorder.

Like the case of Löwenberg and Hill, our cases differ clinically in some respects from those of Merzbacher and Pelizaeus. Without known hereditary trends these differences might appear irreconcilable, but with a definite hereditary occurrence of the disease they lose much of their significance. Clinically, the main point of deviation lies in the age of onset of the first symptoms, which in the cases of Pelizaeus and Merzbacher occurred in the first year of life and in our cases not until the third or fourth decade. Since the age of onset is known to vary greatly in hereditary conditions, this would not necessarily mean that the nervous disorders in these two families differed in nature. In hereditary cere-

bellar ataxia, for example, the symptoms may occur as early as the fifth year and as late as the sixtieth year (Waggoner, Löwenberg and Speicher [6]). In amaurotic idiocy an infantile and a juvenile form are distinguished.

The absence in our patients of a number of symptoms described by Pelizaeus and Merzbacher may also be accounted for by the later appearance of the disease in our cases. To these belong spasticity, particularly of the lower extremities, which became visible in early stages, muscular atrophies, contractures and skeletal deformities. Common to both the American and the German family were ataxia, intention tremor, exaggeration of deep reflexes, loss of umbilical reflexes and moderately advanced mental deterioration. The duration of the disease was longer in Pelizaeus and Merzbacher's patients than in ours, lasting between

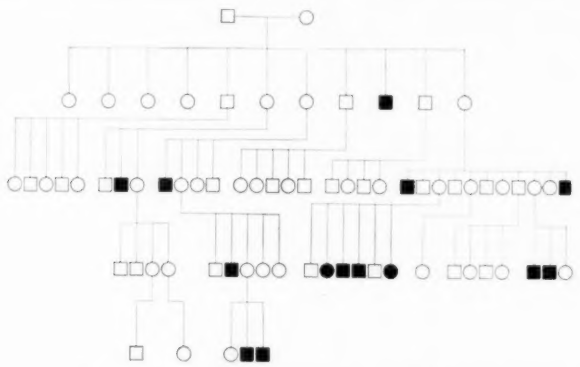

Chart 2.—German family E with Pelizaeus-Merzbacher disease.

twenty and fifty-two years in the former and between twenty and possibly twenty-five years in the latter. The transmission of the disease in Merzbacher's patients was dominant in males and recessive in females (chart 2) and in our cases was dominant in both sexes (chart 1). Most of the patients of Pelizaeus and Merzbacher were males (12 of 14); the mode of transmission was chiefly through unaffected females to males, while the majority of our patients were female (4:1). Although there appear to be some genetic differences, it seems likely that the same gene under different biologic conditions was responsible for the occurrence of the disease in both families.

The disease was pathoanatomically identical in both families.

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6. Waggoner, R. W.; Löwenberg, K., and Speicher, K. G.: Hereditary Cerebellar Ataxia: Report of Case and Genetic Study, Arch. Neurol. & Psychiat. **39**:570 (March) 1938.

INGESTION OF LARGE DOSES OF DILANTIN SODIUM

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Merritt and Putnam [1] have recorded the toxic manifestations that may be associated with the therapeutic use of the anticonvulsant drug dilantin sodium (sodium salt of diphenylhydantoin). The untoward symptoms which might be attributed to the effect of the drug on the nervous system are blurring of vision, diplopia, nausea, dizziness, ataxia and tremor. These symptoms occur in about 15 per cent of patients in the earlier weeks of treatment and usually subside during later treatment. Reactions of the skin and gums have also occurred. We have observed a child afflicted with recurrent attacks of status epilepticus in whom agranulocytic angina developed after the use of 149¼ grains (12.7 Gm.) of dilantin sodium over a period of sixty-seven days. There was no other discernible cause for the blood dyscrasia in this instance, which cleared promptly on withdrawal of the drug and the institution of proper therapy.

This note is concerned with the toxic manifestations incident to enormous doses of the drug. The exhilarating effect obtained from its use appeared to be the main reason that the patient, described in the following case report, took such large amounts.

REPORT OF A CASE

History.—A white boy aged 19, one of fraternal twins, was seen at the psychiatric clinic of the Cincinnati General Hospital on March 21, 1940. There had occurred a gradual change in his personality over a period of five years. Whereas he had been a well behaved boy, he was now a neighborhood nuisance. He had become bitter, antagonistic and uncompromising, and had outbursts of impulsive and destructive behavior. An incident that had occurred six years ago was noteworthy. On Aug. 4, 1934, while working as a caddy, he was struck on the head by a golf ball and rendered unconscious. He was confused for one week after the accident, and his scholastic effort was not as good after the trauma as before. Roentgenograms of the skull taken at that time revealed no bony abnor-

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1. Merritt, H. H., and Putnam, T. J.: Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders, J. A. M. A. **111**:1068-1073 (Sept. 17) 1938.

mality. Four years ago the patient had had his first and only convulsion, of the grand mal type. Since, he had had "queer" spells characterized by a roaring sound in his head and a peculiar feeling of things becoming distant and appearing small. He heard persons speaking to him at these moments, but did not have any idea what was said to him and was unable to talk. After such an episode, during which he did not lose consciousness, he was confused for five to ten minutes. These "spells" had occurred at frequent and irregular intervals.

The patient had drunk heavily since December 1937, in the "spree" fashion. He had participated in about thirty alcoholic bouts since that time, and drank about a pint (473 cc.) of whisky on each occasion. He noted that he did not particularly care for the taste of liquor, and he disliked the burning sensation in the throat and stomach incident to drinking. However, he did approve of the effect. He had not taken alcohol for the past six months.

The results of neurologic examination performed on March 21, 1940 were normal. Because of the history of repeated outbursts of misbehavior the psychiatrist entertained the thought that the patient might have epilepsy. The history of the convulsive seizure, which occurred four years previously, was corroborative evidence, and the outbursts as described conceivably might have fallen within the realm of psychomotor epilepsy. Electroencephalographic studies, done on March 23, 1940, demonstrated occasional periods of slow, high voltage waves. The electroencephalographic record was interpreted as strongly indicating the presence of psychomotor epilepsy.

Because of the extreme effectiveness of the drug in treatment of epilepsy associated with psychomotor equivalents, dilantin sodium was begun on March 28, 1940. The patient was instructed to work up the dose of the drug gradually to 3 capsules, 1½ grains (0.098 Gm.) each, per day and to keep it there.

He was seen again on April 15, 1940, at which time he seemed to be well. He had had no spells since taking dilantin. He returned for a visit at about 4:30 p. m. on April 20, 1940, when it was noted that he staggered. A cursory examination at that time revealed nystagmus, ataxia, tremor, slurring speech and a broad-based, staggering gait. He first denied having taken an overdose of dilantin and later admitted that he had taken about 40 capsules in one dose on that morning. He refused to enter the hospital and was taken home by his parents.

On the evening of April 30, 1940 the patient was admitted to the neurologic service of the Cincinnati General Hospital. At 10 a. m. of that day he began to take large amounts of dilantin sodium. His first dose consisted of about 30 capsules (45 grains [2.925 Gm.]). He supplemented this by more at 11:30 a. m. and at 2 p. m. At 2 p. m. he felt dizzy and light headed, and he noted marked exhilaration. At 4 p. m. he was staggering. At 6 p. m. he took 21 capsules, making a total of about 60 capsules ingested over an eight hour period. He began to be nauseated at 7 p. m. By 8 p. m. the staggering was accompanied by reeling, which was severe, "like a drunken man's." He fell against a telephone pole at about this time and lacerated his forehead. He was vomiting and complaining of frontal headache at the time of his entry to the hospital, at 9 p. m. At this time his vision was blurred, and he noted diplopia. When he stared at an object it "jumped from side to side."

Examination.—Results of physical examination on the evening of April 30 were normal except for a stellate laceration of the forehead just above the right eye and an abrasion of the forehead about the left eye. He preferred to lie flat in bed with his eyes closed. However, he was rather restless.

On neurologic examination several abnormalities were found. The pupils were 5 mm. in diameter, and they reacted through a poor range to flashlight. Hippus

was noted. There occurred rapid horizontal nystagmus on lateral deviation and fixation of the eyes. Diplopia was present on looking in any direction. His speech was rapid and slurred. Words were poorly enunciated, and breaks in the sentence and in words were frequent. All voluntary movement was performed with ataxia, which appeared to be intensified by opening the eyes. He could not sit erect, as he would sway from side to side and the entire trunk would move back and forth in rapid, jerky movement. The tendon reflexes were hyperactive, and the abdominal and cremasteric reflexes were not obtained. There was unsustained ankle clonus. The plantar responses were flexor in type. Sideboards had to be applied to the bed because of the unsteadiness. The patient occasionally appeared to be confused during the first night of his stay in the hospital. He complained of dizziness during the night and vomited on three occasions.

On the morning of May 1 he was still dizzy and nauseated, and he noted that he could not urinate. He had diplopia on looking upward or to the right or left. Marked swinging nystagmus, which was very rapid, was seen when the eyes were deviated to the right, to the left or upward. The pupils still exhibited the hippus phenomenon. He continued to stumble over some words, though his speech had improved. There was moderate ataxia on performing tests of coordination. The cutaneous reflexes were not obtainable.

He vomited once on May 1 and continued to be dizzy on May 2. On the evening of May 2 he was able to retain food and had a fair appetite. He urinated spontaneously on May 2. By May 3 all symptoms and signs had disappeared and he was able to walk unsupported. The results of a neurologic examination on May 4 were completely normal, and he was discharged from the hospital.

The results of laboratory examinations were as follows: On May 1, the urea nitrogen content of the blood was 16 mg. per hundred cubic centimeters, the carbon dioxide–combining power of the blood was 61 volumes per cent and the red blood cell count and hemoglobin concentration were normal. The white blood cell count was 10,100, with 89 per cent neutrophils. Urinalysis, on May 2, gave normal results. He had had no fever during his stay in the hospital.

A lumbar puncture on May 4 revealed an initial pressure of 100 mm. of water. Seven cubic centimeters of cerebrospinal fluid was removed, and the final pressure was 30 mm. The fluid resembled water and contained 1 lymphocyte per cubic millimeter and 48 mg. of protein per hundred cubic centimeters. The colloidal gold curve and the Wassermann reaction were normal.

He returned for another visit on May 27. He had had four "spells" (psychic equivalents) and no dilantin since his discharge from the hospital, on May 4, 1940. He was placed on 1½ grains of dilantin sodium three times a day, and his parents were advised to ration him 1 tablet at each meal.

He was readmitted to the hospital on the evening of June 3, 1940, with a story almost identical with that on his previous admission. He had begun taking large doses of dilantin sodium at 8 a. m. of that day, 2 or 3 capsules at a time. He started out with the idea of taking about 40 capsules (1½ grains each). He stated that he had never noted the "effects" until about four hours after he began to take the capsules. At one time during the day he took 30 capsules at once; his last dose was taken in the receiving ward of the Cincinnati General Hospital, at 6:30 p. m. He took 70 capsules (1½ grains each) in all. He worked at his job as a caddy on the afternoon of June 3. At about 2 p. m. he had a feeling as though he had been drinking whisky (light headed, exhilarated and unrestrained). He became dizzy, staggered somewhat and fell against a tree, lacerating his face and brow. At about 4 p. m. his ears began to "buzz" and a headache developed. One hour later he had diplopia. On his admission to the hospital (6:30 p. m.)

he was perspiring freely and his skin was hot. He complained of dizziness, diplopia and drowsiness. At 7 p. m. he was nauseated.

On admission a laceration of the left brow and multiple abrasions of the face were noted. An incomplete neurologic examination revealed the following abnormalities: He was cooperative but euphoric, lackadaisical and slightly confused. The pupils reacted rather slowly to flashlight. All voluntary movement was incoordinated. The tendon and abdominal reflexes were hyperactive. Unsustained ankle clonus was obtained.

Gastric lavage with 2,000 cc. of physiologic solution of sodium chloride yielded a slight amount of mucus. No evidence of the capsules was present in the washings. He vomited once during the night and the next morning complained of severe generalized headache, pain in the abdomen and extreme nervousness.

A thorough neurologic examination was performed on the morning of June 4. Abnormal findings were vertigo, diplopia, nausea and vomiting. The pupils, which were 5.5 mm. in diameter, reacted promptly and through a moderate range to flashlight. There was a fine horizontal nystagmus when the patient attempted to fix his gaze straight ahead. The nystagmus became much more rapid and coarse on fixing the eyes to the right or the left or upward. Diplopia was noted on looking upward to the left and on attempting to converge. The right eye would diverge during attempts to converge. After several tests for convergence the patient suddenly became extremely nauseated and vomited watery fluid. There were some twitching of muscle fasciculi in the tongue and fine tremor of the whole organ. He maintained the upper extremities extended with a fine tremor and with the eyes closed. He stated that the right extremities were always more affected and weaker than the left after large doses of dilantin. This could not be demonstrated objectively. Slight terminal tremor on finger to nose tests was noted. A moderate rebound phenomenon was present in both upper extremities. The resistance of the extremities to passive movement was decreased. When he attempted to drink, his head and trunk described rapid flexion and extension movements and the cup struck his nose. Tendon reflexes were hyperactive. Only the left lower abdominal reflex was obtained, and it fatigued after several trials. There was a Strümpell sign on the right.

On the evening of June 4 he was able to take fluids without nausea. Up to June 7 he had some difficulty in voiding urine. On June 5 the only remaining abnormal signs were a fine horizontal nystagmus, absence of abdominal reflexes and a Strümpell sign on the right side. He was able to converge the eyes normally. The abdominal reflexes returned on June 8, but the Strümpell sign remained. He was allowed out of bed on June 9 and walked normally. The nystagmus gradually became less marked but was still observable at the time of discharge (June 11). His skin and gums were normal at all times.

The results of significant laboratory tests were as follows: The electrocardiogram was normal. Analyses of urine and stools gave normal results. The white blood cell count on June 4 was 19,100, with 87 per cent neutrophils; on June 5 it was 9,200, with 84 per cent neutrophils, and on June 7 it was 7,750. Otherwise studies of the blood gave normal findings. He had no fever during the eight days in the hospital. On June 4 the prothrombin clotting time (Quick's method) was thirteen seconds. The vitamin C content of the blood was 52 mg. per hundred cubic centimeters. The urea nitrogen of the blood was 17 mg. per hundred cubic centimeters. On June 10 the vitamin C content of the blood was 48 mg. per hundred cubic centimeters. A lumbar puncture was performed on June 6. The initial pressure was 110 mm. of water. Fifteen cubic centimeters of clear fluid

resembling water was removed, and the final pressure was 50 mm. The cerebrospinal fluid contained 1 lymphocyte per cubic millimeter. The protein measured 75 mg. per hundred cubic centimeters, the sugar 67 mg. and the chlorides, as sodium chloride, 722 mg. The colloidal gold curve was normal and the Wassermann reaction negative.

The patient was last seen on July 5, 1940. Since his discharge from the hospital he had returned to his work as a caddy. Both he and his parents had noticed an increase in his irritability. He complained of having at least one "queer spell" daily. Although he realized that his "spells" were controlled by dilantin sodium, he nevertheless refused the medication. This attitude was partly due to his unwillingness to conform to the advice of his parents and physicians. In other words, he refused to have dilantin rationed to him.

It is obvious that the nervous manifestations resulting from large doses of dilantin sodium tend to be the same, though more severe, than those seen in about 15 per cent of patients in the earlier weeks of treatment with therapeutic doses. Nystagmus, blurring of vision, diplopia, nausea, dizziness, ataxia and tremor are common to both states of intoxication. Large doses of dilantin tend to bring out, in addition, signs usually associated with specific involvement of the pyramidal tracts, more marked in the right extremities in this patient (possibly a locus minoris resistentiae, due to the cerebral trauma of six years earlier). The high protein content of the cerebrospinal fluid, 48 mg. per hundred cubic centimeters on May 4 and 75 mg. on June 6, seems noteworthy, as does the leukocytic stimulation.

It is of particular interest that this patient maintains that he has substituted dilantin sodium for whisky in the conduct of his activities. To his way of thinking dilantin affords the same effects as do alcoholic liquors, without the disagreeable burning associated with its ingestion. As he has repeatedly noted, dilantin sodium takes his mind off his worries and gives him "a lift." It is more convenient to take dilantin than whisky, for it may be carried in the pocket and a capsule or two swallowed regardless of one's other activities.

Immediately preceding the second admission to the hospital he was discharged from a job. This caused him considerable worry, and, as he put it, he "tried to drown his worries with dilantin." However, he is employed at present, and he states that he is therefore relieved of worry and of the time in which to become intoxicated (with dilantin or alcohol).

Besides the seizures from which this patient is suffering, he is afflicted with the psychiatric makeup of a "psychopathic personality." Therefore the reasons that he gives for the ingestion of the drug cannot be accepted as entirely valid. The remaining incidents in his history have been corroborated by his family and are considered to be reliable.

On analysis of the patient's behavior it seems that suicide is not the reason for ingestion of dilantin in this case. On all but one occasion

he has maintained that he had not intended to commit suicide. The fact that he took the drug in broken doses over the day tends to corroborate his statement.

He is not addicted to dilantin and was never addicted to alcohol. He was a "spree" drinker, and he has taken dilantin in "spree" fashion. Another factor which is significant is that he has not imbibed alcohol since he has had access to dilantin.

If dilantin sodium in some instances may be substituted for alcohol and the same effects obtained, this hazard had better be known to the physician. The history and findings in the case of this patient afflicted with psychomotor epilepsy and a "psychopathic personality" would indicate that 90 to 105 grain (5.85 to 6.825 Gm.) doses taken over a period of from six to ten hours were just as effective in producing the desired result as an alcoholic debauch.

To our knowledge, these are the largest doses of dilantin sodium ever taken over a short period. It is important to note that these large doses cause no more severe symptoms than an alcoholic bout. The margin of safety of dilantin sodium is accordingly rather large. Large doses of the drug have no sedative or soporific effect, which clearly distinguishes its toxic action from that of the barbiturates.

SUMMARY

The case is recorded of a young man who on three occasions ingested 60, 90.5 and 105 grains (3.9, 5.883 and 6.825 Gm.), respectively, of dilantin sodium over a period of minutes, six hours and ten hours. The chief symptoms were exhilaration, light headedness, dizziness, nausea and vomiting, headache, staggering, diplopia, nystagmus, difficulty in converging the eyes, pupillary abnormalities, ataxia, tremor and changes in reflexes. Of all these signs, nystagmus persisted the longest, and was present for eight days on the last occasion. Significant laboratory findings were the acute elevation of the number of white cells in the blood and an elevation of the cerebrospinal fluid protein.

The reason the patient gave for taking large doses of dilantin sodium was that it was an effective substitute for whisky, particularly because of its exhilarating action.

NOTE.—The patient was readmitted on July 18, 1940, after the ingestion of 57 grains (3.705 Gm.) of dilantin sodium over a period of three hours. His symptoms and clinical course were the same as on his previous admissions. Further analysis of the patient's behavior has led us to believe that the episodes of ingestion of dilantin sodium are suicidal "attempts" manifested in a psychopathic personality.

ELICITATION OF THE "PSEUDOMOTOR CONTRACTURE" IN THE TONGUE BY INTRAMEDULLARY STIMULATION

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MEMPHIS

It has long been known that stimulation of the lingual nerve containing chorda tympani fibers will produce a "pseudomotor contracture" of chronically denervated striated tongue muscle.[1] This response is known as the Philipeaux-Vulpian-Heidenhain phenomenon and is considered to be physiologically identical with the Sherrington contracture as seen in denervated limb muscle, and with the Rogowicz phenomenon [2] as observed in certain denervated facial muscles. The literature pertaining to these phenomena has been reviewed by Hinsey and Gasser [3] Dale,[4] Gasser [5] and Bremer.[6]

Hinsey and Cutting [7] demonstrated that the Sherrington response in the quadriceps and gastrocnemius muscles is produced by stimula-

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1. (*a*) Heidenhain, R.: Ueber pseudomotorische Nervenwirkungen, Arch. f. d. ges. Physiol., 1883, supp., p. 133. (*b*) Philipeaux, J. M., and Vulpian, A.: Note sur une modification physiologique qui se produit dans le nerf lingual par suite de l'abolition temporaire de la motricité dans le nerf hypoglosse du méme côté, Compt. rend. Acad. d. sc. **56**:1009, 1863. (*c*) Vulpian, A.: Nouvelles recherches physiologiques sur le corde du tympan, ibid. **67**:146, 1875.

2. Rogowicz, N.: Ueber pseudomotorische Einwirkung der Ansa Vieussenii auf die Gesichtsmuskeln, Arch. f. d. ges. Physiol. **36**:1, 1885.

3. Hinsey, J. C., and Gasser, H. S.: The Sherrington Phenomenon, Am. J. Physiol. **87**:368, 1928; The Component of the Dorsal Root Mediating Vasodilatation and the Sherrington Contracture, ibid. **92**:679, 1930.

4. Dale, H. H.: Some Chemical Factors in the Control of the Circulation, Lancet **1**:1179, 1233 and 1285, 1929.

5. Gasser, H. S.: Contractures of Skeletal Muscle, Physiol. Rev. **10**:35, 1930.

6. Bremer, F.: Le tonus musculaire, Ergebn. d. Physiol. **34**:678, 1932.

7. Hinsey, J. C., and Cutting, C. C.: The Sherrington Phenomenon: V. Nervous Pathways, Am. J. Physiol. **105**:535, 1933.

tion of postganglionic sympathetic fibers, not by stimulation of somatic motor or sensory fibers. Grant and Kirby [8] produced a typical pseudomotor contracture in denervated tongue muscle of the cat by stimulation of the cervical portion of the sympathetic cord, the chorda tympani and the chorda-lingual nerves. They were unable to obtain the response in the dog on stimulation of the cervical portion of the sympathetic chain. Certainly, the Rogowicz phenomenon may be obtained from stimulation of the cervical portion of the sympathetic cord.[9]

Recently, Lewy, Groff and Grant [9a] obtained what they identified as the pseudomotor response in the cat tongue on stimulation of the mandibular division of the fifth nerve as well as on stimulation of the cervical portion of the sympathetic trunk. On the basis of stimulation and degeneration experiments, they concluded that the fibers mediating this response arise from cranial autonomic neurons located in the mesencephalic nucleus of the fifth nerve the processes of which pass peripherally over both the chorda tympani and the mandibular division of the fifth nerve. Vulpian,[1c] on the other hand, failed to elicit the response on stimulation of the lingual nerve after degeneration of the chorda tympani.

Recent evidence from this laboratory [10] regarding the distribution of mesencephalic root fibers of the fifth nerve and evidence of a definite proprioceptive function for these fibers [11] emphasize the improbability that they are also a part of the cranial autonomic system. Unless antidromic impulses over proprioceptive fibers of much smaller size than those found arising from the mesencephalic root of the fifth nerve can be found to enter those nerves the stimulation of which produces the contracture, the supposition that the Philipeauz-Vulpian-Heidenhain response is the result of stimulation of mesencephalic root fibers is not tenable. It has therefore seemed important to repeat the experiments of Lewy, Groff and Grant, using a more accurate method of locating the mesencephalic root for stimulation and giving particular attention to the criteria which would establish a true lingual pseudomotor response.

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8. Grant, R. P., and Kirby, W. M.: Studies on the Vulpian-Heidenhain Phenomenon, Am. J. Physiol. **123**:79, 1938.

9. (*a*) Lewy, F. H.; Groff, R. A., and Grant, F. C.: Autonomic Innervation of the Face: II. An Experimental Study, Arch. Neurol. & Psychiat. **39**:1238 (June) 1938. (*b*) von Euler, U. S., and Gaddum, J. H.: Pseudomotor Contractures After Degeneration of the Facial Nerve, J. Physiol. **73**:54, 1931. (*c*) Rogowicz.[2]

10. Corbin, K. B.: Observations on the Peripheral Distribution of Fibers Arising in the Mesencephalic Nucleus of the Fifth Cranial Nerve, J. Comp. Neurol. **73**:153, 1940.

11. Corbin, K. B., and Harrison, F.: Function of Mesencephalic Root of Fifth Cranial Nerve, J. Neurophysiol. **3**:423, 1940.

METHODS

Twenty-five adult cats were used in these experiments. All operative procedures were carried out with the animal under anesthesia induced with pentobarbital sodium. The right hypoglossal nerve was sectioned close to its exit from the cranium. Seven to twenty-six days later the animal was prepared for the stimulation experiments. The left hypoglossal nerve was sectioned, a tracheal cannula inserted and the right chorda tympani and lingual nerves exposed. The Horsley-Clarke machine was then affixed to the animal's head. A concentric bipolar electrode, with the tip projecting 0.5 mm. beyond the shield, was used for stimulating. For peripheral stimulation, bipolar silver electrodes were employed, with a tip separation of 4 mm.

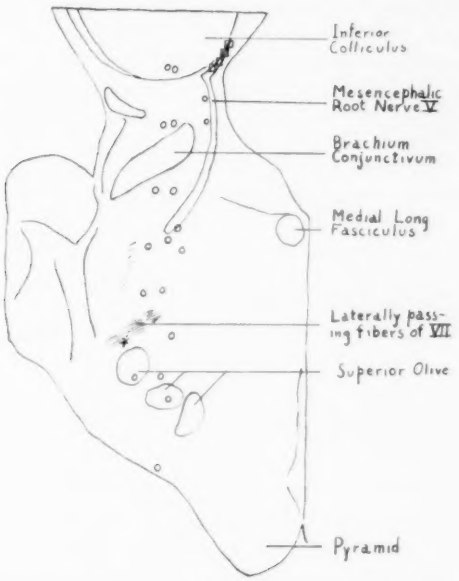

Fig. 1.—Diagram of oblique section through the brain stem of cat 203 at the level of the caudal end of the mesencephalic root of the fifth nerve. Seven experiments.

In this figure and in the accompanying figures, symbols denote response to stimulation. Squares indicate that action potentials typical of the mesencephalic root were obtained when the tip of the electrode was at the point designated and the jaw was depressed. Subsequent stimulation at the same point did not evoke pseudomotor response. Circles denote that stimulation at that point did not evoke a pseudomotor response in the tongue. Plus signs indicate that stimulation at that point evoked a typical pseudomotor response in the tongue.

Various portions of the right mesencephalic root were located oscillographically with the technic previously described;[11] after accurate localization such points were stimulated (figs. 1 to 5). Stimuli, at a rate of about 30 per second, were delivered from the secondary coil of a Harvard inductorium, with 1.5 volts across the primary. The entire brain stem in the neighborhood of the mesencephalic root

and nucleus of the fifth nerve was explored and stimulated, as well as regions around and caudal to the origin and exit of the seventh nerve. Attempts also were made to evoke the pseudomotor response from contralateral intramedullary stimulation.

Each point was first stimulated for approximately two seconds with a coil separation of 12 cm. and the somatic motor response noted (i. e., contraction of muscles of mastication with closure of jaws or contraction of muscles of expression with or without opening of jaws or no response). Excitation with this strength of stimulus was limited to a reasonably small area. The secondary coil was then moved in to a distance of 7 cm., and, with the jaws held open, especial attention was paid to the tongue response. A stimulus strength of this magnitude is required to evoke the pseudomotor response. The stimulus with a coil separation of 7 cm. is so great that stimulation of almost any portion of the pons or mesencephalon results in contraction of muscles supplied by the trigeminal and facial nerves.

At the termination of all experiments the brain was injected with dilute solution of formaldehyde U. S. P. (1:10) removed to solution of formaldehyde U. S. P. and embedded in pyroxylin; serial sections of the mesencephalon and pons were cut at 40 microns and stained according to the Weil technic. All sections were cut approximately parallel to the path of the stimulating electrodes, i. e., in a plane at a 35 degree angle to the vertical plane of the Horsley-Clarke machine (figs. 1 to 3).

RESULTS

Movements of the tongue (curling, arching, elevation, deviation or protrusion) were found to be unreliable in themselves as criteria of the pseudomotor response. Most of these movements may be duplicated by pushing up on the floor of the mouth with a blunt probe. During stimulation they may be the result of contraction of muscles innervated by the seventh and fifth nerves. Contraction of the suprahyoid muscles, especially of the myelohyoid, may cause protrusion and arching of the tongue. It is true that one or more of the aforementioned movements may accompany the pseudomotor contracture, but they, in themselves, should not be considered as constituting the true response.

The pseudomotor response is always accompanied by a certain amount of vasodilatation. This may amount to a brilliant flushing of the tongue or may be so slight as to be difficult to detect. Accompanying the vasodilatation there is usually a certain amount of turgidity of the denervated half of the tongue. When this turgidity is extreme it alone may cause the tongue to arch toward the roof of the mouth and to protrude. Perhaps the most constant and significant evidence of a pseudomotor response is the effect of stimulation on the fibrillation of the degenerating striated muscle. During stimulation there is usually an increase in the rate of fibrillation, lasting for one or two seconds after cessation of stimulation. Following this is a period of inhibition during which fibrillation may be completely absent for as long as ten to fifteen seconds and then slowly reappear.

The turgidity, vasodilatation and effect on fibrillation seem to vary more or less independently of each other in the first month following section of the hypoglossal nerve, but our series of experiments has not been extensive enough to warrant any generalizations in this respect. One definite conclusion is that no response can be called a true pseudomotor contracture unless there is some alteration in the fibrillary contractions both during and after stimulation. Furthermore, it should be noted and stressed that vasodilatation is not in itself evidence of the pseudomotor response. It may be obtained in the normal tongue (3 experiments) on stimulation of the same intramedullary points which yield vasodilatation and the pseudomotor contracture in the denervated tongue.

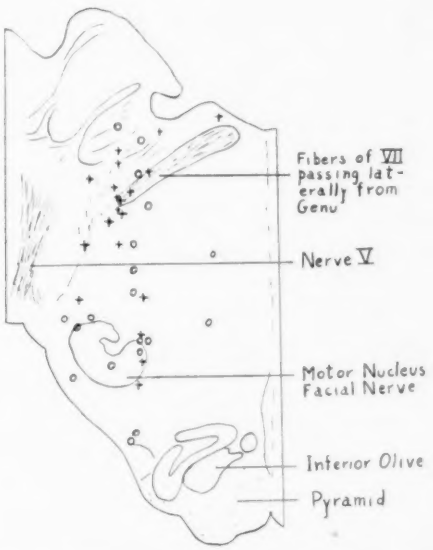

Fig. 2.—Diagram of oblique section through the brain stem of cat 75 at the rostral level of the genu of the seventh nerve. Twelve experiments.

In no experiment (12 cats) did stimulation of the mesencephalic root of the fifth nerve result in a pseudomotor response of the tongue, although subsequent stimulation of the same brain stems caudal to the mesencephalic root and nucleus and with the tip of the electrode within or near the seventh nerve produced a good pseudomotor contracture. There can be no doubt that the tip of the electrode was actually within the mesencephalic root at the time of stimulation with negative responses. We have always recorded a proprioceptive response from such points on depressing the jaw before stimulation, and, as reported previously,[11] this response is obtained only when the tip of the electrode is actually

within the mesencephalic root. Furthermore, subsequent microscopic examination of the brain stem verified the loci (figs. 1 to 5).

When regions caudal to the mesencephalic root were stimulated and when good contraction of the muscles of expression was obtained with a coil separation of 12 cm., indicating that the tip of the electrode was stimulating cells or fibers of the seventh nerve or the reticular matter near them, an excellent pseudomotor contracture of the tongue could be obtained with a coil separation of 7 cm. Subsequent examination of the brain stem revealed that the tip of the electrode was often within, or very close to, the seventh nerve when stimulation produced a tongue contracture (figs. 2, 3, 4 and 5). However, examination of figures 2

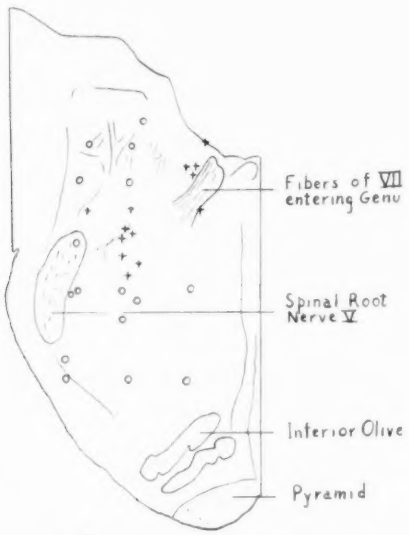

Fig. 3.—Diagram of oblique section through the brain stem of cat 83 at the level of the caudal end of the genu of the seventh nerve. Eight experiments.

and 3 reveals that the response could be elicited also from the reticular matter surrounding the laterally passing fibers of the seventh nerve. Similarly, a few responses were obtained from points close to the seventh nucleus.

Figures 4 and 5 show diagrammatically the points of stimulation of both the mesencephalic root of the fifth nerve and the intramedullary portion of the seventh nerve. In no instance did stimulation of the mesencephalic root of the fifth nerve evoke the pseudomotor response. Stimulation of the laterally passing fibers of the seventh nerve near the caudal end of the mesencephalic root, but not in it, did produce the pseudomotor response.

The pseudomotor contracture was always accompanied by marked salivation. Lacrimation was noted in several instances, but was not specifically looked for in all experiments.

In certain experiments, more than in others, intramedullary stimulation in the region of the facial nerve caused marked vasodilatation. The tongue became flushed with blood on the denervated side and to a lesser degree on the contralateral side. The vasodilatation appeared from two to five seconds after the stimulation began and lasted for about fifteen seconds after stimulation ceased. The flushing was followed by marked

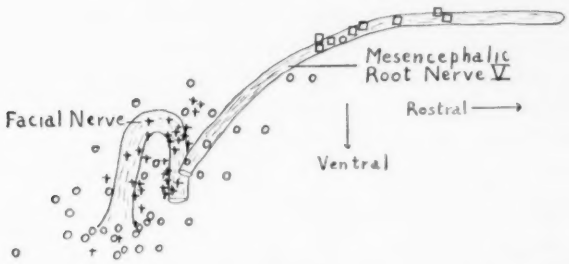

Fig. 4.—Diagrammatic reconstruction of the mesencephalic root of the fifth nerve and the intramedullary portion of the seventh nerve; lateral view. Sixteen experiments.

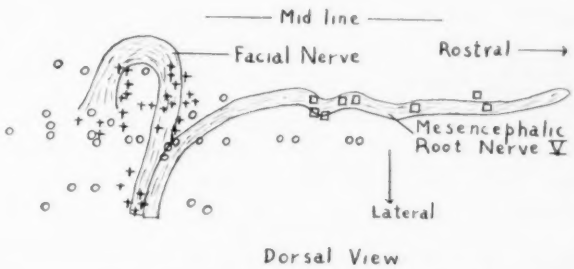

Fig. 5.—Diagrammatic reconstruction of the mesencephalic root of the fifth nerve and the intramedullary portion of the seventh nerve; dorsal view. Sixteen experiments.

blanching, lasting for about ten seconds, and was succeeded by the normal color. It is interesting to note that the inhibition of fibrillation following stimulation persisted until the tongue began to blanch; i. e., fibrillation returned with the disappearance of vasodilatation.

Care had to be exercised to avoid identifying as true active vasodilatation the vascular congestion of the tongue caused by venous stasis accompanying a maintained inspiratory movement during stimulation. It was observed that after venous congestion of the tongue fibrillation was occasionally inhibited for from five to ten seconds, although in these

instances there was no effect on fibrillation during stimulation. In 4 experiments, after production of a pseudomotor response from intramedullary stimulation, the electrode was left in position, the lingual nerve sectioned proximal to its anastomosis with the chorda tympani and stimulation repeated centrally. Such section of the lingual nerve did not abolish or modify the response. If, on the other hand, the chorda tympani nerve was sectioned (9 experiments) and the lingual nerve left intact, a response could no longer be elicited by stimulation of the brain stem at the same point which previously yielded a good contracture. In these experiments a moderate amount of flushing could still be elicited from the opposite half of the tongue (intact side) even with the chorda tympani sectioned on the side of stimulation. This was true also in normally innervated tongues. The pseudomotor contracture, however, was not elicited by contralateral stimulation of the brain stem, i. e., stimulation of the left half of the brain stem in animals whose right hypoglossal nerve had been sectioned.

In 2 experiments, after elicitation of the tongue contracture by central stimulation, the ipsilateral cerebral hemisphere was removed, the trigeminal roots exposed and the mandibular division stimulated. No pseudomotor response was obtained, with even the highest strengths of stimulus.

In none of 12 experiments did stimulation of the cervical portion of the sympathetic trunk produce the pseudomotor tongue contracture.

COMMENT AND CONCLUSIONS

Our results indicate that stimulation of the mesensephalic root and nucleus of the fifth nerve or of the mandibular division of this nerve will not elicit the pseudomotor tongue response. On the other hand, stimulation of the intramedullary portion of the seventh nerve or of the reticular matter which lies between the motor nucleus of the seventh nerve and the genu of this nerve produces a typical pseudomotor response, identical with that obtained by stimulation of the chorda-lingual nerve. The response must be mediated over fibers entering the chorda tympani nerve entirely, since section of the lingual nerve proximal to its anastomosis with the chorda tympani does not abolish the response and section of the chorda tympani does abolish it.

Previous work [11] in which action potentials were recorded from the mesencephalic root and microscopic checks on all stimulation experiments justify the assertion that we stimulated this root specifically without obtaining the pseudomotor response. The fact that the stimuli in strengths required to obtain this response spread to surrounding structures is convincing evidence that the response cannot be obtained from the mesencephalic root and nucleus or adjacent structures. At the same

time, because of the high strengths of stimuli used, it is difficult to say with assurance just what component of the seventh nerve is being activated.

It is highly unlikely that the motor fibers arising in the motor nucleus of the seventh nerve, passing dorsomedially into the genu of that nerve and then laterally, are responsible for this response. These fibers do not enter the chorda tympani nerve. The fibers concerned must either be those of taste, which enter the tractus solitarius, or general visceral efferent fibers passing to smooth muscle or glands in the tongue. As mentioned before, the work of Hinsey and Cutting [7] on the Sherrington phenomenon and that of Rogowicz [2] and von Euler and Gaddum [9b] on the Rogowicz phenomenon indicate that we stimulated cranial autonomic fibers or cells. Bremer and Rylant [12] have shown that the fibers mediating this response in the chorda tympani nerve have a chronaxia of the order of that of autonomic fibers.

If the response is elicited from stimulation of a group of cranial autonomic cells, they are probably located close to the region occupied by the rostral components of the salivatory nucleus,[13] a cranial autonomic group of cells supplying preganglionic fibers to the submaxillary ganglion. Examination of figure 3 shows that the pseudomotor response was elicited a number of times from the reticular matter which lies ventrolateral to the caudal end of the genu of the seventh nerve. The location of the autonomic cells whose fibers enter the seventh nerve activation of which results in lacrimation and vasodilatation is not accurately known.

The fact that we have obtained the pseudomotor response from the genu of the seventh nerve as well as from its laterally passing fibers suggests that the cranial autonomic fibers with which we are dealing enter the seventh nerve before its fibers traverse the genu. However, it must be emphasized that the use of strong shocks, such as we have employed, makes precise localization difficult.

It would seem that we may have stimulated preganglionic cranial autonomic fibers which normally carry vasodilator impulses to the tongue musculature. Vasodilator fibers over the seventh nerve to the pial vessels have been demonstrated.[14] The fact that the pseudomotor response occurs simultaneously with vasodilatation in striated muscle which has

12. Bremer, F., and Rylant, P.: Phénomènes pseudo-moteurs et vasodilatation antidrome, Compt. rend. Soc. de biol. **90**:982, 1924.

13. Papez, J. W.: Comparative Neurology, New York, Thomas Y. Crowell, 1929.

14. Forbes, H. S.; Nason, G. I.; Cobb, S., and Wortman, R. C.: Cerebral Circulation: XLV. Vasodilation in the Pia Following Stimulation of the Geniculate Ganglion, Arch. Neurol. & Psychiat. **37**:776 (April) 1937.

been sensitized by denervation has led many (see Gasser [5] for review) to postulate the same humoral mechanism for both responses.

Stimulation of the brain stem in the regions already noted elicits mild flushing of the contralateral half of the tongue, even when the homolateral chorda tympani nerve has been sectioned. Similar stimulation does not evoke the pseudomotor response in contralateral denervated tongue muscle. If the contralateral flushing is due to intramedullary crossing of vasodilator fibers and the pseudomotor response is produced by stimulation of the same fibers, failure to elicit a contralateral pseudomotor contracture may be due to the crossing of too few fibers. We may postulate that the substance released by these fibers is sufficient to evoke a moderate degree of vasodilatation, but insufficient to elicit the pseudomotor contracture.

Extreme care must be exercised in identifying a lingual response as a true pseudomotor contracture. The criterion of tongue movement, often secondary to contraction of extrinsic striated muscles, is certainly not dependable. The failure to distinguish such "false" responses from the true, in which there is, probably without exception, some effect on fibrillation, may explain the results of Lewy, Groff and Grant,[9a] who claimed to have elicited a pseudomotor contracture from stimulation of the mandibular division of the fifth nerve as well as of the mesencephalic root of that nerve. The observation by these authors of salivation and lacrimation concomitant with the pseudomotor phenomenon would indicate that they were probably stimulating cranial autonomic fibers passing with the seventh nerve, rather than fibers passing in the fifth nerve.

Aside from the experiments of Lewy, Groff and Grant,[9a] there is no evidence that the mesencephalic nucleus gives rise to fibers mediating "impulses for vasoconstriction, lacrimation and salivation." Such responses were never obtained on stimulation of this nucleus, although there can be no doubt that the tip of the electrode was actually within the mesencephalic root and nucleus of the fifth nerve at the time of stimulation. The seventh nerve would appear to mediate all impulses causing lacrimation, while the seventh and ninth nerves (as well as thoracolumbar fibers) mediate impulses activating the salivary glands.

The results here reported make it unlikely that the stimulation of fibers arising in the mesencephalic nucleus of the fifth nerve could produce the pseudomotor contracture in denervated facial muscles (eye and lip phenomena [9a]). Here, again, a more likely explanation is that cranial autonomic fibers over the seventh nerve are responsible for these phenomena.

We have been unable to elicit the Philipeaux-Vulpian-Heidenhain contracture from stimulation of the cervical portion of the sympathetic trunk. In this respect we are in agreement with the observations of

van Rijnberk [15] and of Grant and Kirby [8] on the dog, but not in harmony with those of Lewy, Groff and Grant [9a] or of Grant and Kirby [8] on the cat. This point cannot be definitely settled until the hypoglossal nerve is sectioned intracranially and the possibility of interruption of thoracolumbar fibers from the cervical portion of the sympathetic cord to the hypoglossal nerve is eliminated. In our experiments we endeavored to cut the twelfth nerve as close to its exit from the skull as possible, trying to preserve the sympathetic anastomotic branches, but we cannot be sure that the thoracolumbar fibers to the tongue were not damaged. Here again, however, care must be exercised to avoid interpreting as a true pseudomotor response tongue movements elicited by contraction of adjacent muscles.

SUMMARY

1. In order to locate the origin of fibers mediating the lingual pseudomotor contracture (Philipeaux-Vulpian-Heidenhain phenomenon) and to determine the cranial nerve over which these fibers leave the brain stem, many points in the pons and mesencephalon have been stimulated in 25 cats with chronic sections of the hypoglossal nerve.

2. Stimulation of the mesencephalic root of the fifth nerve or of its mandibular division never gave rise to pseudomotor contracture, as has been claimed by a few investigators.

3. The pseudomotor contracture was elicited by stimulation of the intramedullary portion of the seventh nerve, the reticular matter close to it and the chorda tympani fibers peripherally. Stimulation of these structures also elicited vasodilatation.

4. Section of the chorda tympani nerve abolished the response to intramedullary stimulation; section of the proximal portion of the lingual nerve did not influence the response.

5. The criteria for determining a true pseudomotor response are discussed and the possibilities for error pointed out. The function of the fibers mediating this response is discussed.

15. van Rijnberk, G.: Recherches sur le tonus musculaire et son innervation: I. Actions nerveuses pseudomotrices et innervation du tonus. Première partie: Le phénoméne lingual paradoxal de Vulpian, Arch. neérl. d. sc. exactes et nat. (sect. B) **2**:496, 1917.

SUGAR AND OXYGEN METABOLISM OF THE BRAIN DURING AND AFTER INSULIN HYPOGLYCEMIA

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One of the most widely held theories to explain the improvement reported in the psychoses following metrazol and insulin shock therapy is that the respiration of the brain is stimulated. Gerard [1] suggested that the cerebral hypoxia which occurs during the metrazol convulsion or insulin hypoglycemia is followed by a period of "overshooting," i. e., hyperactivity with increased oxygen consumption by the brain, which may depend on liberation of potassium from the interior of the neuron. According to the investigations of Gerard and Magoun,[2] a moderate increase in external potassium ions acts as a great stimulus to neural activity. Although cerebral hypoxia occurs during the metrazol convulsion [3] and insulin hypoglycemia,[4] there is no adequate evidence that increased respiration of the brain follows the depression of metabolism. Whether the increased electrical activity exhibited by the brain when deprived of oxygen or sugar or when exposed to cyanide or other chemicals can be interpreted as an increase in cerebral respiration is open to question.[5]

From the Division of Psychiatric Research, Boston State Hospital.

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1. Gerard, R. W.: Anoxia and Neural Metabolism, Arch. Neurol. & Psychiat. **40**:985 (Nov.) 1938.

2. Gerard, R. W., and Magoun, H. W.: Influence of Potassium and Calcium on Motor Discharges, Proc. Soc. Exper. Biol. & Med. **34**:755 (June) 1936.

3. (*a*) Himwich, H. E.; Bowman, K. M.; Fazekas, J. F., and Orenstein, L. O.: Effect of Metrazol Convulsions on Brain Metabolism, Proc. Soc. Exper. Biol. & Med. **37**:359 (Nov.) 1937. (*b*) Loman, J.; Rinkel, M., and Myerson, A.: Metrazol Convulsions: Changes in Oxygen, Carbon Dioxide and Sugar Contents of Arterial and of Internal Jugular Venous Blood, Arch. Neurol. & Psychiat. **43**: 682 (April) 1940.

4. Dameshek, W., and Myerson, A.: Insulin Hypoglycemia: Mechanism of the Neurologic Symptoms, Arch. Neurol. & Psychiat. **33**:1 (Jan.) 1935. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Brain Metabolism During Hypoglycemic Treatment of Schizophrenia, Science **86**:271 (Sept. 17) 1937.

5. Gerard, R. W.: Response of Nerve to Oxygen Lack, Am. J. Physiol. **92**: 498 (March) 1930; Studies on Nerve Metabolism: Respiration in Oxygen and Nitrogen, ibid. **82**:381 (Oct.) 1927; footnote 1.

Chemical data, which have been used to substantiate the theory of stimulation of cerebral metabolism, are also inadequate. The fact that after the metrazol convulsion the level of oxygen in the peripheral venous blood may be changed does not indicate an altered consumption of oxygen by the brain.[3b] Changes in oxygen content of blood coming from the brain and those of blood from the arm or leg in various metabolic disturbances do not necessarily parallel each other. To estimate the uptake of oxygen by the brain at a given time, both the arterial blood and the blood coming directly from the brain must be simultaneously analyzed. Furthermore, interpretation of arteriovenous differences in oxygen content must take into consideration possible changes in blood flow. The same statements hold true for changes in sugar consumption.

The present study was carried out to determine by the chemical method whether after insulin hypoglycemia there is evidence of increased respiration of the brain.

MATERIAL AND METHOD

Subjects with dementia praecox of the passive and cooperative type were utilized. The patients came to the laboratory in the morning with breakfast withheld. Determinations of the sugar and oxygen content were made on blood withdrawn from the brachial artery and the internal jugular and basilic veins or from the artery and the internal jugular vein alone. After specimens of blood were collected under basal conditions, moderate to large doses of insulin (60 to 100 units) were injected intravenously. At the height of the insulin reaction samples were again collected. The subjects were then given 100 Gm. of dextrose by mouth in order to aid recovery from the hypoglycemic state. At half-hour intervals blood was again collected, so that the patients were followed for one to two hours after the administration of the dextrose. Thus, from these samples the brain uptake or the comparative brain and arm uptakes of sugar and oxygen before, at the height of and during the period of recovery from the hypoglycemic state were determined. No experiment was accepted for analysis unless the blood from the artery and that from the veins were withdrawn simultaneously and with a minimum of discomfort to the patient.

The blood sugar was determined by the method of Folin and Wu, readings being made in the Evelyn photocolorimeter. The oxygen content was determined by the method of Van Slyke and Neill.

RESULTS

Comparison of the Sugar Uptake by the Brain and that by the Arm (9 cases; table 1).—The uptake of dextrose by the brain and that by the arm were compared in 9 experiments. Moderate to marked perspiration and drowsiness occurred in every case. Twitchings and convulsions were absent. The sugar level of arterial blood at or about the height of the insulin reaction (forty-five minutes after the injection of insulin) varied between 32 and 65 mg. per hundred cubic centimeters. At this time the arterial–jugular venous difference in dextrose content

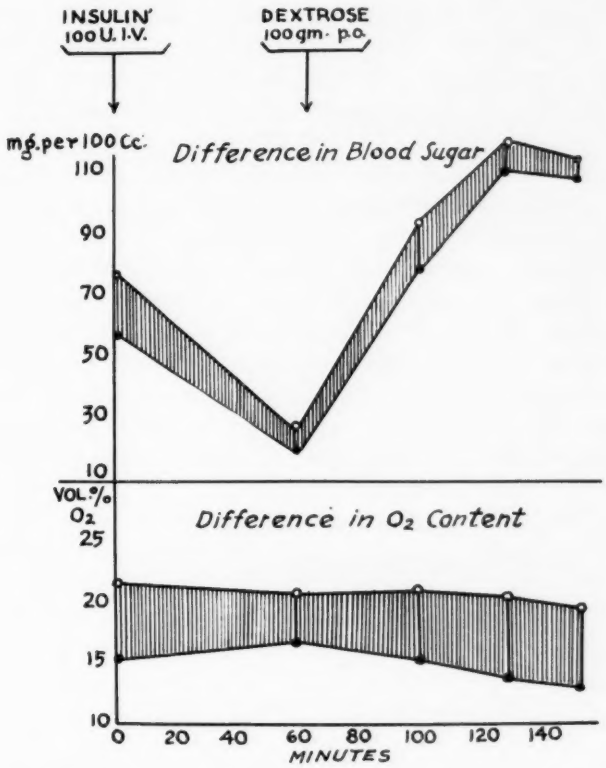
of the blood was greatly diminished in all but 2 instances. In the latter (cases 2 and 5) the arterial sugar had fallen to a level of only 65 and 55 mg., respectively. Similarly, the arterial—basilic venous difference in sugar became greatly reduced, except in case 2.

After the administration of dextrose, several interesting phenomena occurred. The sugar level of arterial blood reached maximal levels at the half-hour or one hour period and then began to fall toward normal levels in 7 cases. In the other 2 cases the rise in arterial sugar was sluggish, obviously due to poor absorption of the administered dextrose.

TABLE 1.—*Arterial–Jugular Venous (A-J) and Arterial–Basilic Venous (A-B) Differences in Blood Sugar Content During Hypoglycemia and During the Period of Recovery Following Administration of Dextrose*

Case			Basal Content, Mg. per 100 Cc.	Height of Insulin Reaction, Mg. per 100 Cc.	Sugar Content, Mg. per 100 Cc., After Administration of Dextrose, Minutes			
					30	60	90	120
1	J. H.	A-J	13	— 1	0	2	— 4	5
		A-B	5	— 3	17	35	13	17
2	M. A.	A-J	18	12	11	1	20	4
		A-B	11	11	18	2	19	3
3	T. D.	A-J	17	1	31	6	13	—
		A-B	10	1	52	59	28	—
4	T. D.	A-J	22	— 2	13	10	7	—
		A-B	3	11	24	32	20	—
5	J. T.	A-J	16	14	— 4	6	15	—
		A-B	10	5	5	26	29	—
6	S. N.	A-J	14	7	10	4	6	—
		A-B	10	2	7	9	5	—
7	L. M.	A-J	19	2	7	12	—	—
		A-B	10	— 3	21	35	—	—
8	S. N.	A-J	10	3	1	6	—	—
		A-B	6	9	13	3	—	—
9	L. M.	A-J	21	7	— 3	— 7	—	—
		A-B	7	2	24	24	—	—

Despite the return of the arterial blood sugar to normal or higher than normal levels in the 7 cases, the uptake of sugar by the brain and arm became increased over the basal figures in only 1 instance (case 3), and then only temporarily. At the completion of the experiments, the uptake of sugar by the arm was greater than that of the brain; that is, the original relationship was reversed, except in 3 cases, in which they were both about equally depressed. In some instances, at certain periods after the administration of the dextrose, the arteriovenous differences fluctuated, usually to the disadvantage of the brain. Finally, in 6 of the 9 cases the uptake of sugar by the brain, and in 3 cases the uptake of sugar by the arm, was definitely less than before the induction of the hypoglycemia.



Arterial–jugular venous differences in blood sugar content (milligrams per hundred cubic centimeters) and oxygen content (volumes per cent) during hypoglycemia and during the period of recovery following the administration of dextrose.

In this figure, the curve for arterial blood is represented by a line and hollow circles; that for blood from the internal jugular vein, by a line and solid circles.

TABLE 2.—*Arterial–Jugular Venous (A-J) Differences in Blood Sugar Content and in Oxygen Content During Hypoglycemia and During the Period of Recovery Following Administration of Dextrose*

		Sugar, Mg. per 100 Cc.					Oxygen, Volume per Cent				
				After Administration of Dextrose, Minutes					After Administration of Dextrose, Minutes		
	Case	Basal Content	Height of Insulin Reaction	30	60	90	Basal Content	Height of Insulin Reaction	30	60	90
1	J. T.	26	1	9	— 5	— 6	5.5	6.2	5.7	5.0	5.8
2	L. M.	20	8	16	10	6	6.7	4.1	5.5	6.7	6.3
3	J. T.	13	— 3	17	2	17	7.8	7.1	5.5	7.0	8.8
4	J. T.	18	11	15	5	6	8.7	7.0	6.2	4.8	6.3
5	T. D.	21	1	2	—	—	7.7	3.9	4.2	—	—

Relationship Between the Sugar and the Oxygen Uptake by the Brain (5 cases; figure; table 2).—A similar procedure was followed in these experiments, except that both the oxygen and the sugar content were analyzed in the arterial and the internal jugular venous blood. Forty-five minutes after the injection of 60 to 100 units of insulin, the arterial blood sugar varied between 20 and 27 mg. per hundred cubic centimeters. At this time the arterial–jugular venous difference in sugar was moderately to markedly reduced in each instance, and in 4 of the 5 cases a reduction in oxygen uptake occurred simultaneously. During the period following the administration of dextrose, however, the uptake of sugar and that of oxygen did not always run parallel. Thus, at certain periods the arterial–jugular venous difference in dextrose became greatly diminished, while the uptake in oxygen remained unchanged or became increased over a previous level. Or, when the uptake in sugar rebounded toward its original level the uptake in oxygen did not necessarily follow in the same direction.

In general, the brain showed a poor tendency to recover so far as its uptake of sugar was concerned, so that in 4 of 5 instances the arterial-jugular venous difference was greatly reduced from original levels. Furthermore, at the completion of the experiments, the arterial–jugular venous difference in oxygen either had returned to original levels or was still diminished, except in 1 case, in which it had returned to a level slightly higher than the original.

COMMENT

That changes in blood flow do not explain the arteriovenous differences in oxygen content during insulin hypoglycemia has been directly demonstrated by Loman and Myerson[6] and by Leibel and Hall.[7] Indirect evidence that the changes in sugar and oxygen are unrelated to possible changes in blood flow is the disproportional alteration in the level of these substances, both during and after the period of hypoglycemia. A change in blood flow should result in a similar and proportional alteration in the uptake of sugar and of oxygen by the brain. The dissimilar and disproportional changes in the consumption of oxygen and of sugar further suggest that the important role attributed to hypoxia in insulin hypoglycemia may be exaggerated and that the important or essential change is reduced consumption of sugar by the brain, a deficiency which directly or indirectly may bring about alterations in the mental state.

6. Loman, J., and Myerson, A.: Studies in the Dynamics of the Human Craniovertebral Cavity, Am. J. Psychiat. **92**:791 (Jan.) 1936.

7. Leibel, B. S., and Hall, G. E.: Cerebral Blood Flow Changes During Insulin and Metrazol (Pentamethylenetetrazol) Shock, Proc. Soc. Exper. Biol. & Med. **38**:894 (June) 1938.

That an altered consumption of sugar by the brain is not common to other forms of shock therapies must also be stressed. For example, during the metrazol convulsion, although a rise in blood sugar occurs, the brain continues to take up its usual quota of this fuel. Furthermore, the metrazol convulsion is not followed by an increased uptake of oxygen by the brain, even though there is hypoxia during the attack.[3b]

The results of the present experiments indicate that the brain either recovers its original capacity to utilize sugar and oxygen soon after the insulin hypoglycemia or is delayed in this recovery. On the other hand, muscle recovers more actively than the brain after it has been deprived of sugar. Such a reaction might be expected, since the brain is sensitive to lack of sugar, which is probably its only or essential fuel, and therefore is more readily disturbed than muscle. The degree of impaired neural function probably depends on the degree of lowered concentration of sugar and the length of time the brain is deprived of this essential fuel. On these factors, as well as others still unknown, will depend how quickly and completely the brain recovers from the effects of hypoglycemia. In prolonged and severe degrees of hypoglycemia, it may be predicted that the brain will recover even more slowly than is evident in the present study.

These data support the conclusion that the beneficial clinical effects observed after insulin therapy and other forms of shock treatment cannot be attributed to increased respiration of the brain. It is not unlikely that the common change resulting from the shock therapies is injury to the brain, either reversible or irreversible. That cerebral injury commonly occurs in man and animals after large doses of insulin and repeated metrazol convulsions has been shown by many investigators.[8]

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8. Zimmerman, H. M., and Yannet, H.: The Histopathology of the Cerebral Changes Following Prolonged Insulin Hypoglycemia, to be published. Grayzel, D. M.: Changes in the Central Nervous System Resulting from Convulsions Due to Hyperinsulinism, Arch. Int. Med. **54**:694 (Nov.) 1934. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467 (March) 1938. Bowen, B. D., and Beck, G.: Insulin Hypoglycemia, Ann. Int. Med. **6**:1412 (May) 1933. Moersch, F. P., and Kernohan, J. W.: Hypoglycemia: Neurologic and Neuropathologic Studies, Arch. Neurol. & Psychiat. **39**:242 (Feb.) 1938. Appel, K. E.; Alpers, B. J.; Hastings, D. W., and Hughes, J.: Central Nervous System Changes Produced by Insulin, Am. J. Psychiat. **96**:397 (Sept.) 1939. Hassin, G. B.: Cerebral Changes in Fatal Cases Following Treatment with Barbital, Soluble Barbital U. S. P., Insulin and Metrazol, Arch. Neurol. & Psychiat. **42**: 679 (Oct.) 1939. Davis, P. A., and Sulzbach, W.: Changes in the Electroencephalogram During Metrazol Therapy, ibid. **43**:341 (Feb.) 1940. Winkelman, N. W., and Moore, M. T.: Neurohistopathologic Changes with Metrazol and Insulin Shock Therapy: An Experimental Study on the Cat, ibid. **43**:1108 (June) 1940.

SUMMARY AND CONCLUSIONS

Comparative determinations of the sugar and oxygen uptake of the brain and of the arm were carried out on a group of subjects with dementia praecox during and after insulin hypoglycemia, with the following results:

1. During the hypoglycemia the uptake of sugar by the brain was always diminished. The uptake of oxygen was simultaneously diminished. These changes are explained on the basis of actual decreased cerebral consumption of these substances, rather than on the basis of changes in blood flow.

2. After the administration of dextrose the brain showed a lag in recovering its capacity to utilize sugar. The arm, on the other hand, usually recovered this function much more vigorously than the brain. A change in uptake of oxygen by the brain did not always parallel the change in uptake of sugar during the same period.

There is from these data no evidence that sugar and oxygen metabolism of the brain is stimulated after insulin hypoglycemia. On the contrary, neural dysfunction, rather than stimulation of cerebral respiration, may be the important factor which is related to the change in mental states of subjects treated by insulin hypoglycemia or other forms of shock.

Dr. Abraham Myerson, director of research of the Boston State Hospital, gave advice and assistance in this study.

EFFECTS OF INSULIN AND METRAZOL THERAPY ON CEREBROSPINAL FLUID PROTEINS

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Certain pathologic alterations in the brain are known to be associated with changes in cerebrospinal fluid protein. It is of interest therefore to determine whether similar changes might be caused by the action of insulin and metrazol. That cerebrospinal fluid proteins are affected by insulin has been suggested by the work of Nicolajev.[1] The present study was undertaken for the purpose of measuring and evaluating such changes, not only for insulin but for metrazol as well.

METHOD

Insulin.—Patients with schizophrenia were subjected to insulin[2] treatment for about five hours per day six times a week. Doses of insulin varied from 50 to 300 units. Spinal punctures were made one to five days before treatment to obtain control specimens. After at least five successive days of treatment, specimens of cerebrospinal fluid were taken within one to two hours after injection of insulin to determine its more immediate effect. When patients had been treated from one to six months, spinal punctures again were made three to one hundred and ten days after the last injection of insulin to determine whether the changes produced were permanent.

Metrazol.—To study the immediate effect of metrazol, two specimens of spinal fluid were withdrawn, one immediately before the injection of 0.3 to 0.8 grains (19.5 to 52 mg.) of metrazol and the other about two hours after the start of the reaction. In another group of subjects spinal punctures were made two to twenty-six days after the last shock to study later effects of metrazol. Members of this group had received treatment for varying periods.

Controls.—The effect of successive spinal punctures on concentration of protein in the cerebrospinal fluid was determined by collecting specimens at two hour intervals from untreated patients.

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1. Nicolajev, V.: Ueber die Bromdurchlässigkeit der Hirnschranken, insbesondere bei schizophrenen Erkrankungsformen, Ztschr. f. d. ges. Neurol. u. Psychiat. **157**:206, 1937; A Special Glial Alteration After Repeated Insulin Shock in Animals, Am. J. Psychiat. **94** (supp.):302 (May) 1938.

2. Eli Lilly & Co. furnished the insulin (iletin) used in this study.

TABLE 1.—*Changes in Cerebrospinal Fluid Proteins Before, During and After Insulin Treatment*

	(A) Before Insulin					(B) During Insulin*					(C) After Insulin					
Case No.	Length of Illness, Months (1)	Albumin, Mg. per 100 Cc. (2)	Globulin, Mg. per 100 Cc. (3)	Total Protein, Mg. per 100 Cc. (4)	A/G Ratio (5)	Time After First Treatment, Days (6)	Albumin, Mg. per 100 Cc. (7)	Globulin, Mg. per 100 Cc. (8)	Total Protein, Mg. per 100 Cc. (9)	A/G Ratio (10)	Treatment, Length of Previous Days (11)	Time Since Last Days (12)	Albumin, Mg. per 100 Cc. (13)	Globulin, Mg. per 100 Cc. (14)	Total Protein, Mg. per 100 Cc. (15)	A/G Ratio (16)
1	6	24.0	7.0	31.0	3.4	73	20.0	21.0	41.0	1.0	..	..	...	...	...	...
2	4	32.8	8.7	41.5	3.8	30	26.2	10.3	36.5	2.5	..	..	...	...	...	...
3	6	15.7	3.3	19.0	4.8	5	14.8	6.7	21.5	2.2	—	—	—	—	—	—
4	48	29.2	9.3	38.5	3.1	7	25.0	10.0	35.0	2.5	—	—	—	—	—	—
5	6	16.8	5.7	22.5	3.0	8	13.3	6.3	19.6	2.1	—	—	—	—	—	—
6	8	24.5	8.0	32.5	3.1	11	17.7	7.3	25.0	2.4	—	—	—	—	—	—
7	6	15.4	6.6	22.0	2.3	11	18.8	7.8	26.6	2.4	—	—	—	—	—	—
8	4	22.0	6.0	28.0	3.7	13	23.9	8.6	32.5	2.8	—	—	—	—	—	—
9	10	12.0	5.0	17.0	2.4	15	12.2	7.3	19.5	1.7	71	15	13.8	6.7	20.5	2.1
10	3	30.0	10.0	40.0	3.0	16	26.3	8.7	35.0	3.0	31	6	25.3	6.7	32.0	3.8
11	4	12.5	10.0	22.5	1.3	23	22.2	11.3	33.5	2.0	58	37	19.0	6.0	25.0	3.2
12†	4	29.3	8.7	38.0	3.4	23	27.8	10.7	38.5	2.6	41	9	29.3	5.7	35.0	5.1
13	10	16.0	8.0	24.0	2.0	27	13.2	4.3	17.5	3.1	89	3	24.5	7.0	31.5	3.5
14	24	11.0	3.0	14.0	3.6	31	14.8	7.7	22.5	1.9	171	110	14.3	5.7	20.0	2.5
15	6	—	—	—	—	32	11.2	7.3	18.5	1.5	68	7	9.3	6.7	16.0	1.4
16	2	—	—	—	—	55	12.3	6.7	19.0	1.8	62	4	35.8	6.7	42.5	5.3
17	1	—	—	—	—	60	27.5	10.0	37.5	2.8	72	12	39.3	6.7	46.0	5.8
Average....		21.2	7.1	28.2	3.1	(cases 1 to 14)	19.8	9.1	28.9	2.2						
						(cases 9 to 17)	18.6	8.2	26.8	2.3			23.4	6.4	29.8	3.7
Difference of (A) and (B) (cases 1 to 14)..						.....	+ 1.4	— 2.0	— 0.7	+0.9	(B)—(C)	(9 to 17)	— 4.8	+1.8	— 3.0	—1.4
Standard error of the difference of (A) and (B).....						.....	± 2.49	± 1.22	± 3.10	±0.28		(B) and (C)	± 4.36	±0.78	± 4.79	±0.57

* All specimens taken one to two hours after injection of insulin.

† Patient previously treated with metrazol.

The method used for the determination of total protein was a modification of that of Andersch and Gibson.[3] Sodium sulfate was used to precipitate globulin according to a procedure to be published elsewhere. Specimens containing red blood cells in excess of the few normally present were discarded.

RESULTS

Insulin (table 1).—When average figures for this group are compared it is apparent that during treatment there is a drop in the albumin-

TABLE 2.—*Changes in Cerebrospinal Fluid Proteins Before Treatment and Two Hours After Initial Metrazol Shock*

	(A) Before Metrazol Shock				(B) Two Hours After Metrazol Shock			
Case No.	Albumin, Mg. per 100 Cc.	Globulin, Mg. per 100 Cc.	Total Protein, Mg. per 100 Cc.	A/G Ratio	Albumin, Mg. per 100 Cc.	Globulin, Mg. per 100 Cc.	Total Protein, Mg. per 100 Cc.	A/G Ratio
1	26.0	18.0	44.0	1.5	19.0	21.0	40.0	0.9
2	38.0	12.0	50.0	3.2	27.0	12.0	39.0	2.3
3	15.0	7.0	22.0	2.2	10.0	6.0	16.0	1.7
4	13.0	7.0	20.0	1.9	11.0	9.0	20.0	1.2
5	16.0	7.0	23.0	2.3	12.0	11.0	23.0	1.1
6	16.0	5.0	21.0	3.2	15.0	7.0	22.0	2.1
7	38.4	6.6	45.0	5.8	21.2	7.3	28.5	2.9
8	23.2	8.3	31.5	2.8	23.0	9.0	32.0	2.6
9	21.2	7.3	28.5	2.9	17.7	7.3	25.0	2.4
10	26.8	4.7	31.5	5.7	26.8	6.7	33.5	4.0
11	26.5	7.0	33.5	3.8	23.2	7.3	30.5	3.2
12	25.5	10.0	33.5	2.6	23.0	11.0	35.0	2.2
13	15.3	5.7	21.0	2.7	12.2	7.3	19.5	1.7
14	16.5	7.0	23.5	2.4	17.0	8.0	25.0	2.1
15	37.7	8.3	45.0	4.4	27.3	8.7	36.0	3.1
16	11.8	6.7	18.5	1.8	10.5	7.0	17.5	1.5
17	6.4	3.6	10.0	1.8	5.4	2.6	8.0	2.1
18	19.5	7.0	26.5	2.8	15.0	6.5	21.5	2.3
19	13.2	8.3	21.5	1.6	13.2	8.3	21.5	1.6
20	16.2	6.3	22.5	2.6	17.3	6.7	24.0	2.6
21	19.7	4.3	24.0	4.6	19.2	4.3	23.5	4.5
22	12.8	4.7	17.5	2.7	10.3	3.7	14.0	2.8
23	18.7	6.3	25.0	3.0	18.7	6.3	25.0	3.0
24	15.5	6.0	21.5	2.6	15.5	6.0	21.5	2.6
25	15.0	5.0	20.0	3.0	16.0	5.0	21.0	3.2
26	36.3	8.7	45.0	4.2	36.3	8.7	45.0	4.2
Average.....	20.8	7.2	27.9	3.0	17.9	7.8	25.7	2.4
Difference of (A) and (B).....					+ 2.9	—0.6	+ 2.2	+0.6
Standard error of the difference of (A) and (B).....					± 2.18	±0.88	± 2.65	±0.29

globulin ratio (0.9 ± 0.28) which is highly significant. The albumin-globulin ratio of the cerebrospinal fluid decreased in 10 patients, increased in 2 and remained unchanged in 2. Ten of 14 patients showed a rise in globulin, which averaged 28 per cent for the whole group. The change falls just short of statistical significance. Albumin decreased in 9 patients, increased in 4 and remained unchanged in 1. The mean concentration of albumin decreased during treatment, but again the change was not significant, owing mainly to important exceptions to the prevalent response.

3. Andersch, M., and Gibson, R. B.: The Colorimetric Determination of Plasma Proteins, J. Lab. & Clin. Med. **18**:816 (May) 1933.

TABLE 3.—*Changes in Cerebrospinal Fluid Proteins Before and After Metrazol Treatment*

	(A) Before Metrazol					(B) After Metrazol					
						Treatment					
Patient	Length of Illness, Months	Albumin, Mg. per 100 Cc.	Globulin, Mg. per 100 Cc.	Total Protein, Mg. per 100 Cc.	A/G Ratio	Time After First Days	Time Since Last Days	Albumin, Mg. per 100 Cc.	Globulin, Mg. per 100 Cc.	Total Protein, Mg. per 100 Cc.	A/G Ratio
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
D. K.	6	13.3	6.7	20.0	2.0	4	4	19.2	6.3	25.5	3.1
M. B.	6	15.3	5.7	21.0	2.7	7	4	22.3	6.7	29.0	3.3
S. G.	6	16.0	7.0	23.0	2.3	7	2	16.0	5.0	21.0	3.2
B. S.	9	11.3	5.7	17.0	2.0	11	4	15.5	6.0	21.5	2.6
J. K.	48	13.0	5.0	18.0	2.6	14	4	38.4	6.6	45.0	5.8
S. B.	24	13.0	5.0	18.0	2.6	16	3	20.2	7.3	27.5	2.8
R. P.	12	18.7	6.3	25.0	3.0	21	3	16.5	7.0	23.5	2.4
M. I.	9	26.5	7.0	33.5	3.8	21	4	25.3	5.7	31.0	4.4
M. M.	9	13.8	5.7	19.5	2.4	21	16	15.5	6.0	21.5	2.6
J. M.	6	11.0	8.0	19.0	1.4	22	7	16.0	6.0	22.0	2.7
D. A.	12	13.0	7.0	20.0	1.9	24	2	17.0	4.0	21.0	4.3
M. F.	2	20.2	7.3	27.5	2.8	26	2	22.3	6.7	29.0	3.3
R. S.	24	16.2	6.3	22.5	2.6	30	5	10.5	5.0	15.5	2.1
E. H.	18	23.2	8.3	31.5	2.8	45	2	20.8	6.7	27.5	3.1
F. M.	10	15.0	7.0	22.0	2.2	60	26	16.0	4.0	20.0	4.0
E. C.	36	15.5	7.0	22.5	2.2	60	3	19.7	4.3	24.0	4.3
B. O.	6	13.2	8.3	21.5	1.6	60	4	18.2	6.3	24.5	2.9
Average		15.8	6.7	22.5	2.4			19.4	5.9	25.3	3.3
Difference of (A) and (B)								— 3.6	+0.8	— 2.8	—0.9
Standard error of the difference of (A) and (B)								± 1.74	±0.35	± 1.92	±0.27

After treatment was discontinued the albumin-globulin ratio rose in 8 patients and remained unchanged in 1. In some patients the albumin-globulin ratios at this stage exceeded 5.0. Total protein rose markedly in 3 patients and moderately in 1. Small decreases were observed in 4 patients, while a large decrease occurred in 1. On the whole, a significant rise occurred in the albumin-globulin ratio (1.4 ± 0.57) and a significant fall in globulin (1.8 mg. ± 0.78 mg. per hundred cubic centimeters). Changes in total protein and albumin were not statistically significant.

Metrazol (table 2).—Twenty-six patients not previously treated who presented a definite reaction to metrazol (convulsive seizure) showed a significant drop in the albumin-globulin ratio (0.6 ± 0.29) two hours after the initial metrazol shock. Within the group, 16 of the

TABLE 4.—*Effect of Successive Spinal Punctures on Cerebrospinal Fluid Proteins (No Medication)*

	(A) First Specimen				(B) Second Specimen, Collected Two Hours Later			
	Albumin, Mg. per 100 Cc.	Globulin, Mg. per 100 Cc.	Total Protein, Mg. per 100 Cc.	A/G Ratio	Albumin, Mg. per 100 Cc.	Globulin, Mg. per 100 Cc.	Total Protein, Mg. per 100 Cc.	A/G Ratio
Average of 10 cases	22.3	7.7	30	3.0	22.6	7.3	29.9	3.1
Maximum	36.7	11.3	46	4.4	35.7	9.3	45.0	4.4
Minimum	11.3	5.7	17	1.3	12.3	5.0	18.0	2.1
Difference of (A) and (B)					− 0.3	+0.4	+ 0.1	−0.1
Standard error of the difference					± 3.29	±0.74	± 3.61	±0.40

26 patients showed a marked decrease in the albumin-globulin ratio, 8 little or no change and 2 a rise. The fall in the albumin-globulin ratio was caused by a decrease in albumin and an increase in globulin, although in neither fraction was the change statistically significant. Four patients failed to react to metrazol and showed a high albumin-globulin ratio, which did not change after treatment.

The later effects of metrazol on cerebrospinal fluid proteins are shown in table 3. The specimens examined were obtained four to sixty days after beginning the treatment and from two to twenty-six days after the last injection of metrazol. In contrast to the lowering of the albumin-globulin ratio, which appears to be the predominant immediate effect of metrazol, an increase was observed subsequent to treatment in 15 to 17 patients. In this group a significant rise in albumin (3.6 ± 1.74 mg. per hundred cubic centimeters), a highly significant rise in the albumin-globulin ratio (0.9 ± 0.27) and a significant fall in globulin (0.8 ± 0.35 mg. per hundred cubic centimeters) occurred. The change in total protein was not significant.

No correlation could be noted between the changes in cerebrospinal fluid protein and clinical improvement.

Controls.—Of a group of 10 untreated control subjects (table 4), 6 showed no change in the albumin-globulin ratio, an increase occurred in 3 and a decrease appeared only once. In the last case the change differed from that following drugs, since no change occurred in globulin. Changes in the 10 untreated control subjects were without statistical significance. The mean values for total protein, albumin, globulin and albumin-globulin ratio before and after treatment were practically identical.

COMMENT

It appears from the changes observed that there were alterations in the volume of cerebrospinal fluid and in the permeability of the blood-cerebrospinal fluid barrier following administration of insulin or metrazol. A decrease in the cerebrospinal fluid protein would follow transfer of water from blood plasma to the perivascular spaces. Such a transfer probably is associated with the severe anhydremia following administration of insulin observed by Drabkin and Edwards [4] and others in animals and by Butt and Keys,[5] Koppelman [6] and Zozaya [7] in schizophrenic patients. Drabkin and Ravdin [8] observed a rise in cerebrospinal fluid pressure prior to insulin convulsions in dogs, a change that may accompany increase in volume. Qualitative changes represented by the altered albumin-globulin ratio indicate that protein also was added to the cerebrospinal fluid. The source of protein so added is not apparent, although increase in capillary permeability due to anoxia is a possibility. Presumably, sufficient protein is added to the cerebrospinal fluid to counterbalance the increase in volume. A passive mechanism of this type would, however, require increases in volume of 440 per cent during insulin shock and of about 375 per cent after metrazol shock to reduce the albumin-globulin ratio from 3.1 to 2.2 and 2.9 to 2.3, respectively, while the total protein was maintained constant. Consequently, the assumption of an augmented secretion of a fluid containing more globulin may provide a more acceptable explanation.

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4. Drabkin, D. L., and Edwards, D. J.: The Production of Anhydremia with Insulin, Am. J. Physiol. **70**:273 (Oct.) 1924.

5. Butt, J. R., and Keys, A.: Effect of Large Doses of Insulin on the Proteins and the Colloid Osmotic Pressure of Blood Serum, Arch. Int. Med. **63**:156 (Jan.) 1939.

6. Koppelman, S.: The Effects of Large Doses of Insulin on Blood Hydration in Man, Am. J. M. Sc. **197**:78 (Jan.) 1939.

7. Zozaya, J.: Physicochemical Changes in Blood Serum of Patients with Schizophrenia Treated by Hypoglycemic Shock, Proc. Soc. Exper. Biol. & Med. **37**:327 (Nov.) 1937.

8. Drabkin, D. L., and Ravdin, I. S.: The Mechanism of Convulsions in Insulin Hypoglycemia, Am. J. Physiol. **118**:174 (Jan.) 1937.

It is of interest that similar changes are observed after infection of the meninges, namely, increase in volume and decrease in the albumin-globulin ratio.

SUMMARY

Both insulin and metrazol caused appreciable changes in the cerebrospinal fluid proteins of schizophrenic patients. The immediate effect of metrazol was a lowering of the albumin-globulin ratio. Later, after one to eight weeks of treatment and a rest of three to four days, the albumin and albumin-globulin ratio increased, while the globulin decreased. Insulin caused a rise in globulin and a depression of the albumin-globulin ratio; when the treatment was discontinued the albumin and albumin-globulin ratio returned to higher values, while globulin decreased.

ROLE OF TRAUMA IN AMYOTROPHIC LATERAL SCLEROSIS

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Trauma has been considered often as an etiologic factor in the production of amyotrophic lateral sclerosis. In a review of the literature Jelliffe [1] collected 94 cases with a history of trauma. Starker [2] found a traumatic incidence of approximately 10 per cent in 79 cases and Cramer [3] one of 11 per cent in 34 cases. Erb [4] critically analyzed 43 cases and came to the conclusion that trauma was of etiologic significance. Brouwer [5] has stated that under certain conditions an injury may cause amyotrophic lateral sclerosis. The clinical evidence in many cases is so impressive as to suggest that trauma should be considered a factor; yet since these conclusions are based on clinical observations only, the etiologic role of trauma may be regarded as doubtful. The answer to the question whether trauma can cause amyotrophic lateral sclerosis or a syndrome with a course like that of typical amyotrophic lateral sclerosis is important both from a theoretic and from a practical standpoint.

Pathoanatomic examination in a number of cases of amyotrophic lateral sclerosis with a history of trauma has failed to reveal a definite relationship between the injury and the neuropathologic changes (Adamkiewicz,[6] Eisenlohr,[7] Nonne,[8] Brouwer,[9] Anglada,[10] Wenderowic

From the Neuropsychiatric Institute, University of Michigan; R. W. Waggoner, M.D., Director.

Read at the Sixty-Fifth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 6, 1939. An abstract and discussion of the paper were published in the Transactions of the American Neurological Association, 1939.

1. Jelliffe, S. E.: J. Nerv. & Ment. Dis. **82**:415 and 532, 1935.
2. Starker, W.: Deutsche Ztschr. f. Nervenh. **46**:483, 1913.
3. Cramer, C. P.: Neurol. Centralbl. **10**:616, 1891.
4. Erb, W.: Deutsche Ztschr. f. Nervenh. **45**:1, 1912.
5. Brouwer, B., cited by Jelliffe.[1]
6. Adamkiewicz, S.: Charité-Ann. **5**:353, 1880.
7. Eisenlohr, C.: Ztschr. f. klin. Med. **1**:435, 1880.
8. Nonne, M.: Neurol. Centralbl. **25**:973, 1906.
9. Brouwer, B.: Geneesk. bl. u. klin. en lab. v. d. prakt. **15**:101, 1910.
10. Anglada, J.: Montpellier méd. **33**:73, 1911.

and Nikitin,[11] Ottonello,[12] Gerber,[13] Schmidt,[14] and van Bogaert, Ley and Nyssen [15]). The only dissenting opinion is that of Hassin,[16] who examined a case which we consider to be one of amyotrophic lateral sclerosis, but he interpreted his findings as of traumatic origin. Since the role of trauma in this disorder has received so much attention, without proof of its significance, we present a case in which there is histologic evidence of both injury to the spinal cord and amyotrophic lateral sclerosis, with no apparent relationship between the two.

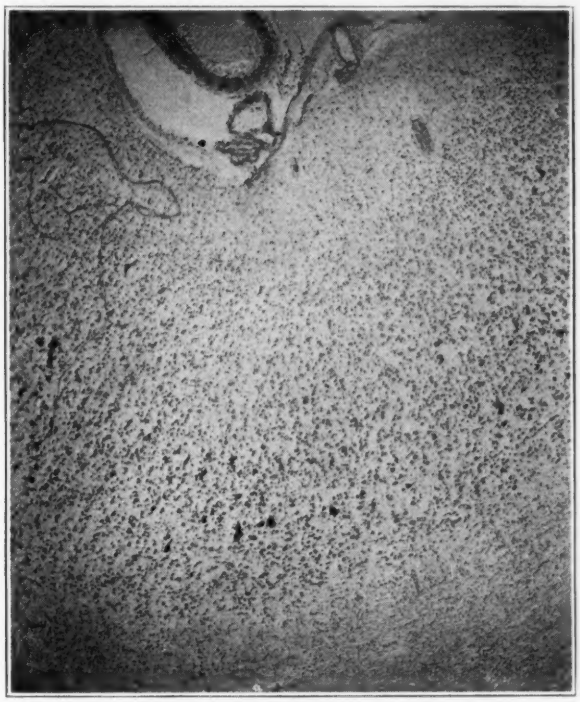

Fig. 1.—Cortex of the motor region with a few remaining degenerated giant pyramidal cells. Nissl stain.

11. Wenderowic, E., and Nikitin, M.: Arch. f. Psychiat. **52**:300, 1913.

12. Ottonello, P.: Rassegna di studi psichiat. **18**:221, 1929.

13. Gerber, J.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **17**:13, 1931.

14. Schmidt, G.: Thesis, Leipzig, 1931.

15. van Bogaert, L.; Ley, R. A., and Nyssen, R.: Acta psychiat. et neurol. **7**:873, 1932.

16. Hassin, G.: Concussion of the Spinal Cord, Arch. Neurol. & Psychiat. **10**: 194 (Aug.) 1923.

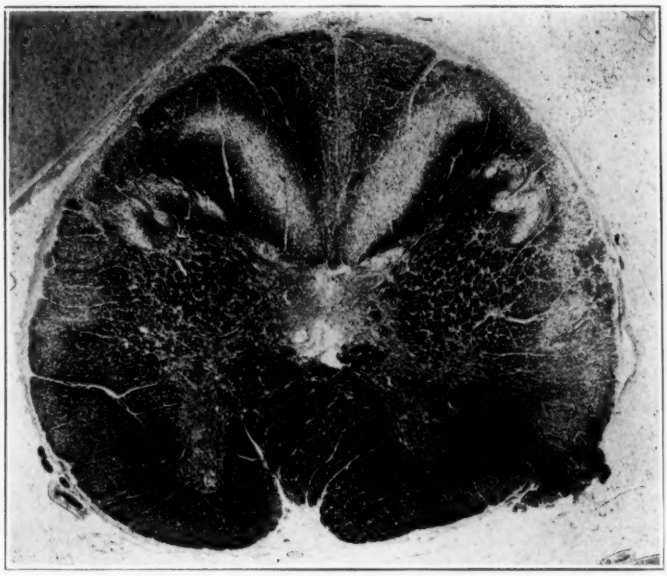

Fig. 2.—Section through the level of decussation showing: (1) moderate degeneration of the partly crossed pyramidal tracts, (2) retrograde degeneration of the cerebellar tracts and (3) severe degeneration of the funiculi cuneatus and gracilis. Weigert stain.

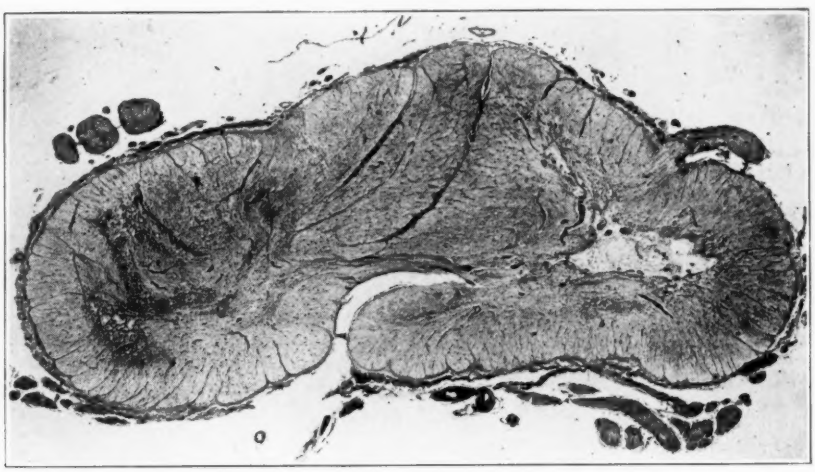

Fig. 3.—Section through the region of the injury, showing a large focus of softening in the right lateral column and a similar, but smaller, lesion in the left. The gray matter on the right is destroyed; on the left it is still faintly visible. Mallory's stain.

REPORT OF A CASE

History.—A white man aged 66 was admitted to the University Hospital, complaining of difficulty in walking, weakness of both arms and pain in the right shoulder. Five years before admission there developed tremor and progressive weakness of both arms. He was able to continue his work as a farmer until one

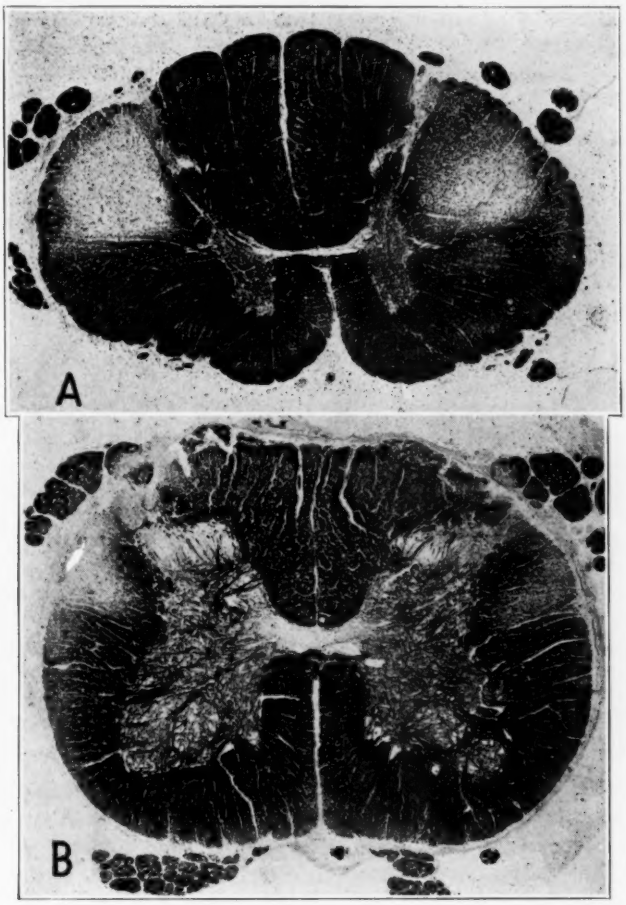

Fig. 4.—*A,* section through the thoracic region, showing severe degeneration of both crossed pyramidal tracts. *B,* section through the lumbar region, with degeneration of both pyramidal tracts. Weigert stain.

and one-half years before admission, at which time he fell from a height of 12 feet (365 cm.). After the fall he was unable to move his arms or legs but gradually regained the use of his extremities. A year before admission to the hospital he was able to walk as much as half a mile (804 meters), but about that time he began to have more weakness of his extremities, most marked in the left arm and leg. He also complained of muscular tremors accompanied by pain

in the right shoulder and arm and a tingling sensation in the right leg. In the six months before admission his voice became hoarse and easily fatigued.

Examination on admission revealed moderate atrophy of the muscles of the face and tongue with fibrillary tremors in the latter. There was marked atrophy of the interossei muscles and of the thenar and hypothenar eminences, more marked in the right hand. Partial flexor contractures were present in the joints of the elbow, wrist and hand. There were fibrillary tremors associated with weakness and atrophy of the muscles of both arms and shoulders and of the chest. There was hypalgesia over the first to the twelfth dorsal segment on the right side, with no definite changes on the left. There was definite increase in tone of

Fig. 5.—Section through the cervical region above the injury, showing reduction of the anterior horn cells. Van Gieson stain.

the muscles of the extremities. Hoffmann's sign was positive bilaterally. The biceps and triceps reflexes were hyperactive on both sides. The knee jerks were hyperactive and there was a positive Babinski sign on the right. The patient walked with an ataxic gait. Roentgenologic examination demonstrated an old, distinct compression fracture of the second and third cervical vertebrae with fusion of the bodies but no displacement and a similar fracture of the eighth dorsal vertebra with some discoloration. Examination of the spinal fluid gave negative results except for a 4 plus reaction for globulin. Slight mental changes were noted and were considered to be associated with cerebral arteriosclerosis. The patient became progressively weaker; difficulty in swallowing developed, and he died of aspiration pneumonia six weeks after admission to the hospital. The approximate duration of the neurologic symptoms was six years.

Autopsy.—The important observations were chronic bilateral fibrocaseous pulmonary tuberculosis, patchy pneumonia, generalized atherosclerosis and diffuse fibrosis of the myocardium. There was an old compression fracture of the bodies of the second and third cervical and the eighth dorsal vertebrae. The cerebral vessels were atherosclerotic. The brain showed moderate bilateral atrophy of the motor region.

Histologic Examination.—The large pyramidal cells of the motor cortex were greatly reduced in number or were entirely absent in many of the sections (fig. 1). In the pons there was moderate demyelination of both pyramidal tracts. At the level of the decussation there were moderate degeneration of both pyramidal tracts, severe degeneration of the funiculus cuneatus and partial destruction of the funiculus gracilis, the last being limited to the segments above the injury (fig. 2), and degeneration of both spinocerebellar tracts, the ventral one being more involved on the right. The effects of the trauma were clearly visible in the fourth, fifth and sixth cervical segments, where the cord was distorted and flattened and presented a curved anteromedial fissure (fig. 3). On the right side an irregular area of softening destroyed the entire gray matter and central portion of the lateral column, while on the left a similar lesion destroyed most of the pyramidal tract and a part of the gray matter, leaving the outlines of the latter partially visible. The funiculi gracilis and cuneatus were mildly involved (fig. 3). Below the injury, and extending throughout their length, there were severe degeneration of the crossed pyramidal tracts and moderate degeneration of the direct tracts (fig. 4). The anterior horn cells in the cervical, thoracic and lumbar segments were considerably reduced (fig. 5). Throughout the degenerated areas there were accumulations of lipoid material, both free and in scavenger cells. The neurons in the nuclei of the ninth and twelfth cranial nerves were shrunken and reduced in number.

COMMENT

Careful analysis of the pathoanatomic changes leads us to believe that there were two independent conditions present, the one associated with trauma, the other amyotrophic lateral sclerosis. The entire motor system was degenerated, commencing with the giant pyramidal cells of the precentral gyri, the degeneration extending throughout the length of the cerebrospinal tracts with the exception of the white matter of the hemispheres and the internal capsule. This finding is not uncommon in cases of amyotrophic lateral sclerosis (Noto[17]). Often there is a variation in the intensity of the degeneration in different parts of the motor system. The reduction and degeneration of the neurons in the nuclei of the ninth and twelfth cranial nerves and in the anterior horns of the spinal cord, both below and above the injury, are typical alterations in cases of amyotrophic lateral sclerosis. It is more difficult to interpret the degeneration of the posterior funiculi above the point of injury. Segmental impairment of these tracts has been reported in cases of amyotrophic lateral sclerosis by Davison and Wechsler.[18] On the other

17. Noto, G. G.: Riv. di pat. nerv. **34**:910, 1930.

18. Davison, C., and Wechsler, T. S.: Amyotrophic Lateral Sclerosis with Involvement of Posterior Column and Sensory Disturbances, Arch. Neurol. & Psychiat. **35**:229 (Feb.) 1936.

hand, since the degeneration of the posterior columns in our case was limited to the cervical segments it could be attributed to the injury, but in any case the true solution of this point is irrelevant. The traumatic changes in the spinal cord were easily differentiated from those caused by the preexisting disease process, and they resembled the post-traumatic lesions described by Schmaus [19] and many others. As might be expected, the degeneration of the pyramidal tracts was more severe below the level of the injury, apparently being accentuated by the latter.

The presence of atrophy of the muscles of the thenar and hypothenar eminences, the shoulders and the upper and lower extremities together with tremors, exaggerated reflexes and the Babinski sign constitute the typical clinical picture of amyotrophic lateral sclerosis. As the disease progressed bulbar symptoms, such as hoarseness, atrophy of the muscles of the tongue and lips and difficulty in swallowing, were noted. The first symptoms of the disease commenced several years before the trauma and increased in severity until the time of death. Unfortunately, little is known about the early stages of the disease or the post-traumatic period, as the patient did not consult a physician. We have his statement that in spite of the severity of the accident and its post-traumatic symptoms he recovered from these rather promptly and again became ambulatory. The course of the amyotrophic lateral sclerosis did not seem to be appreciably altered by the trauma, and he survived the injury for eighteen months. Bulbar symptoms did not develop until a year after the accident.

Hassin has described a case which appears to us to be one of amyotrophic lateral sclerosis in a person who had a minor trauma four weeks before the onset of the first symptoms. The histologic changes in his case were degeneration of the anterior horn cells and of the crossed pyramidal tracts associated with microscopic softenings in the gray matter, most marked in the cervical region. Because of the absence of degeneration of the direct pyramidal tracts or of the anterior commissure and the presence of the softenings, he concluded that the lesions in his case differed from those in amyotrophic lateral sclerosis. Pollock, in his discussion of Hassin's paper, pointed out that the clinical picture in Hassin's case seemed typical of amyotrophic lateral sclerosis and not of concussion. The majority of patients with severe concussion may live only a few weeks, according to Schmaus,[19] Jakob [20] and others. In Hassin's case the degeneration of the pyramidal tracts was assumed to be secondary to the destruction of the neurons in the ventral horns. He compared the degeneration of the pyramidal tracts to that observed in pellagra, but, as Pollock has pointed out, the degeneration in the latter

19. Schmaus, H.: Virchows Arch. f. path. Anat. **122**:326, 1890.

20. Jakob, A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **51**:247, 1919.

condition is axonal. In the discussion on Hassin's paper, Patrick commented that if degeneration of the lateral tracts is secondary to destruction of the anterior horn cells, it is unusual that it is not found in cases of anterior poliomyelitis. Hassin suggested that preservation of the uncrossed pyramidal tracts would be against the diagnosis of amyotrophic lateral sclerosis, but such is not necessarily the case. It is well known that the pyramidal tracts may be unevenly affected and may show little degeneration in some of the segments. Occasionally even the crossed pyramidal tracts are only slightly involved, even below the decussation, and one tract may be more severely affected than the other. Hassin stated that the most conclusive evidence in favor of a traumatic origin in his case was the microscopic softenings. This, however, does not indicate trauma, as it has been seen by these authors and others in typical cases of amyotrophic lateral sclerosis in which there was no history of trauma (Noto;[17] Büscher[21]).

It is our opinion that the clinical observations, the pathologic changes reported in the literature and the clinicopathologic study in our case offer no conclusive evidence that trauma can cause amyotrophic lateral sclerosis or a syndrome which follows a similar typical clinical course.

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21. Büscher, J.: Arch. f. Psychiat. **66**:61, 1922.

LYMPHOGRANULOMATOSIS (HODGKIN'S DISEASE) OF THE NERVOUS SYSTEM

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The recognition of neurologic signs and symptoms during the course of Hodgkin's disease has called to our attention the need for more careful correlation between the clinical and the pathologic aspects of all cases of lymphogranulomatosis. Ginsburg [1] called attention to the paucity of information in textbooks of neurology regarding the involvement of the central nervous system in Hodgkin's disease. There are, however, numerous reports in the literature to indicate that such involvement occurs more frequently than is recognized generally.

In not an inconsiderable percentage of cases of Hodgkin's disease there is as the initial, and occasionally only, manifestation evidence of involvement of the central or peripheral nervous system. This observation is of diagnostic importance. The first of the 2 case reports in this paper illustrates the necessity of a careful evaluation of widely distributed neurologic signs and symptoms, which may be the earliest indication of Hodgkin's disease.

Seventeen cases of Hodgkin's disease, in 16 of which the patients were admitted to the Jewish Hospital from 1912 to 1940, are here reviewed with reference to implication of the nervous system. Two cases are reported in detail, 1 presenting the unusual occurrence of lymphogranulomatous meningoencephalopathy and involvement of the spinal cord and brachial plexus and the other illustrating the usual form of invasion of the spinal epidural space.

REPORT OF CASES

CASE 1.—L. A., a woman aged 44, was admitted to the Jewish Hospital in September 1939 (service of Dr. H. L. Goldburgh), in a stuporous condition and presenting left hemiparesis.

Read before the American Association of Neuropathologists, Rye, N. Y., June 6, 1940.

From the John L. Eckel Laboratory of Neuropathology, University of Pennsylvania Graduate School of Medicine, and the Jewish Hospital.

1. Ginsburg, S.: Hodgkin's Disease, with Predominant Localization in the Nervous System: Early Diagnosis and Radiotherapy, Arch. Int. Med. **39**:571 (April) 1927.

The patient had been admitted to the hospital on two previous occasions, the first being on April 22, 1938, with the diagnosis of menopausal syndrome. She complained of sharp pains in both legs and in the right shoulder, severe headaches, photophobia, double vision and vertigo, and indigestion of fifteen years' duration. Her temperature fluctuated from 98 to 101 F. daily. No cervical adenopathy was seen. Roentgenographic examination of the chest revealed nodules at the roots of both lungs and infiltration of the right subclavicular zone suggestive of a malignant process.

She was admitted for the second time on Jan. 27, 1939. There was apparent cervical, axillary and inguinal adenopathy. The spleen and liver were palpable. A tentative diagnosis of lymphoblastoma was made. The temperature was of the

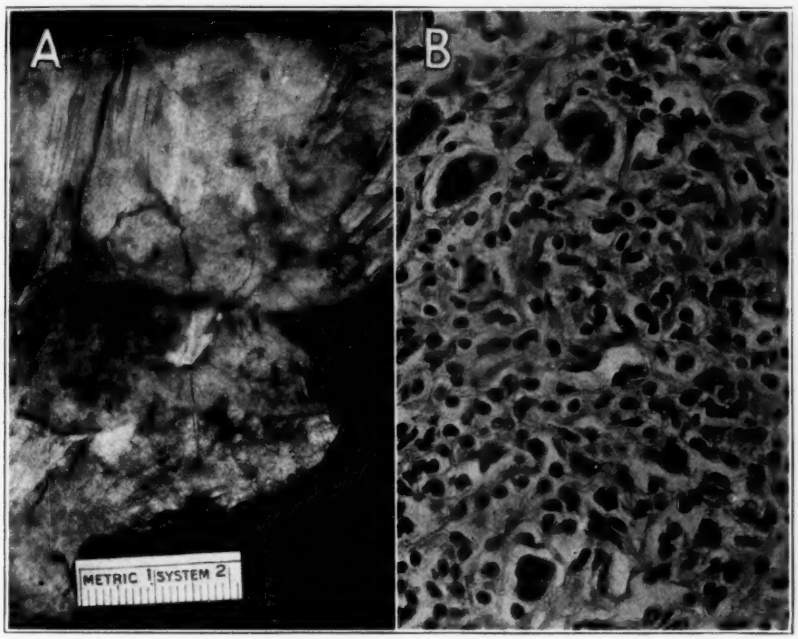

Fig. 1.—*A*, portion of dura from the right cerebral hemisphere illustrating discrete and confluent subdural lymphogranulomatous plaques, which attain a thickness of 1.5 mm. Plaques occurred on the cranial surface as well, but did not exceed 0.5 mm. in thickness. *B*, section through a dural plaque shown in *A*, indicating the lymphogranulomatous character of the tissue with lymphogenous elements and fibrous connective tissue stroma predominating and numerous Sternberg-Reed cells. Hematoxylin and eosin stain; × 400.

Pel-Ebstein type and varied from 97.2 to 102.6 F. The positive neurologic findings were: (1) marked atrophy of the muscles of the entire left upper limb; (2) hypalgesia in the distribution of the ulnar and median nerves on the left side; (3) absence of the left triceps reflex; (4) hypalgesia of the left leg from the groin to the toes, and (5) analgesia over the third, fourth and fifth sacral dermatomes on the right side. Biopsy of an inguinal lymph node showed the fibrous stage of Hodgkin's disease. Roentgenograms of the chest revealed a mass in the hilus

of the left lung and a smaller one in the hilus of the right lung. There was evidence of involvement of some of the dorsal vertebrae. The blood count showed persistent anemia, anisocytosis and poikilocytosis; the differential count was normal. The platelet count was 97,200. Roentgen therapy was instituted and continued after her discharge, on March 12, 1939, but pain in both legs and arms and in the back continued.

When admitted to the hospital for the last time the patient was dull and stuporous and unable to cooperate. The temperature was 100 F., the pulse rate 90 and the respiratory rate 20. She was greatly emaciated, and the lymphadenopathy was very apparent. The liver was palpable. On September 11 the neurologic status was as follows: (1) The head and eyes were turned to the right; (2) there were complete palsy of the left facial nerve, of central type, and left hemiparesis with almost complete flaccid palsy of the left upper limb; (3) the tendon reflexes were exaggerated bilaterally, more so on the left, and (4) the Hoffmann sign, Babinski sign and ankle clonus were present bilaterally, all more pronounced on the left. The patient died Sept. 13, 1939.

Autopsy revealed lymphadenopathy of the cervical, axillary, inguinal, peribronchial and mesenteric lymph nodes. The spleen weighed 200 Gm., and on sectioning showed an irregular surface, with a nodular, infiltrating neoplastic process. The liver weighed 1,100 Gm., was congested and showed no areas of infiltration.

Gross Examination of the Brain and Meninges.—A portion of the dura (fig. 1 *A*) showed flat, irregular masses on both surfaces, mainly, however, on the cerebral surface. Some of the masses were discrete, while others were confluent, forming a wide plaquelike band across the dura. These varied in thickness to the extent of 1.5 mm. The margins of the plaque could be stripped away from the dura.

The leptomeninges were slightly thickened and somewhat opalescent. There was some blood pigment over the motor, premotor and temporal lobes of both hemispheres.

The vessels at the base of the brain were slightly hypoplastic and fibrotic.

Section through the pons, medulla and cerebellum revealed a mild degree of congestion.

Coronal section of the brain, at the level of the tip of the temporal lobe, revealed subcortical softening in the first frontal convolution on the right side. The cortex and subcortex showed congestion. As one proceeded caudally, the entire subcortical area, including the superior lateral portions of the caudate nucleus and putamen, was seen to be involved by this softening. At the level of the optic chiasm the internal capsule was also involved by softening and the subcortex had a peculiar stippled, moth-eaten appearance. At the level of the substantia nigra the lateral nucleus of the thalamus showed a stippled type of softening.

Microscopic Examination.—The dura showed invasion of lymphogranulomatous tissue over both the outer and the inner surface. The lymphogenous elements were densely arranged and enmeshed in a dense fibrous connective tissue stroma. Numerous Sternberg-Reed cells were irregularly interspersed in this tissue (fig. 1 *B*). The leptomeninges were mildly fibrotic and contained a small number of phagocytic elements but no inflammatory cells. The pial vessels were congested, and some free blood was seen in the subarachnoid space.

Gross inspection of the sections stained for myelin sheaths revealed severe demyelination with a moth-eaten appearance, involving mainly, though not exclu-

sively, the white matter of the rostral half of the right cerebral hemisphere. This extended beyond the limits of the centrum ovale, invading the cortex as well. The basal ganglia were also involved, particularly the caudate nucleus and the putamen. Many of the areas of patchy demyelination were confluent, so that whole stretches of brain substance were demyelinated (fig. 2). The lenticular nucleus, thalamus and hypothalamus were involved on both sides (fig. 3). The occipital lobes, cerebellum and brain stem showed either minimal involvement or none at all.

Fig. 2.—Myelin sheath stain of a coronal section of the right hemisphere at the level of the tip of the temporal lobe, showing the spotty and confluent demyelination of the cortex, centrum ovale, striate body, internal capsule and corpus callosum. Weil stain; × 1¾.

The Nissl preparations also showed great variability in the involvement of the cortex and subcortex. In and about the areas of intense demyelination the cell stains revealed the most marked changes. The cortex showed severe loss of ganglion cells, with glial replacement, formation of new vessels and the presence of many rod cells. The subcortex showed areas of softening with numerous gitter cells, multinucleated glia cells. gemästete glia and Sternberg-Reed cells.

Many of the vessels showed perivascular cuffing with gitter cells, lymphocytes and an occasional plasma cell (fig. 4). The fat stain (Herxheimer) confirmed

the presence of phagocytes. With the Cajal stain the astrocytes were seen to be greatly increased in number and undergoing both progressive and regressive changes. Several areas, in the vicinity of softenings, showed large clusters of Hortega cells. The Sternberg-Reed cells were widely scattered, though frequently they were observed in small groups. These cells were of either the giant uninuclear or the multinuclear type, as described by Sternberg [2] and by Reed [3] (fig. 5). The cell stains showed extensive damage to the subcortical ganglia. Within the pons an occasional area similar to that in the cerebrum was noted. The medulla was relatively uninvolved. The cerebellum showed only an occasional area, involving mainly the white matter.

Fig. 3.—Myelin sheath stain of a coronal section of the left hemisphere at the level of the mammillary bodies, illustrating the extensive spotty demyelination of the white substance and subcortical ganglia. Weil stain; × 1½.

The small vessels in the cortex and subcortex showed swelling of the endothelial cells and at times a feeble effort at formation of new vessels. The larger vessels showed changes mainly in the media, with thinning of this coat and metachromatic staining.

A microscopic diagnosis of lymphogranulomatous invasion of the dura and brain was made.

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2. Sternberg, C.: Ueber eine eigenartige unter dem Bilde der Pseudoleukämie verlaufende Tuberculose des lymphatischen Apparates, Ztschr. f. Heilk. **19**:21, 1898.

3. Reed, D. M.: On the Pathological Changes in Hodgkin's Disease, with Especial Reference to Its Relation to Tuberculosis, Johns Hopkins Hosp. Rep. **10**:133, 1902.

The history in this case illustrates how readily the initial symptoms of lymphogranulomatous invasion of the nervous system may be overlooked or explained away by some concomitant or nonexistent condition. The diagnosis on the patient's first admission to the hospital was menopausal syndrome and chronic gastritis. The latter diagnosis may be

Fig. 4.—Cellular stain of a section similar to that shown in figure 2, showing the usual cellular reaction encountered in the degenerated areas. Note the perivascular cellular cuffing, composed of naked nuclei, occasional lymphocytes, gitter cells and a rare plasma cell. Huge numbers of gitter cells and gemästete glia can easily be made out in this illustration. The large cells with heavily staining masses of chromatin are the uninuclear and multinuclear Sternberg-Reed cells. Toluidine blue stain; × 92.

pardoned on the basis of a history of digestive disturbances over a period of fifteen years. The former probably served as a mask for the many symptoms of neurologic origin, such as sharp pains in both legs

and the right shoulder, headaches, photophobia, double vision and vertigo, which represented in all probability the first manifestations of Hodgkin's disease. On the second admission, in January 1939, the diagnosis was established clinically and pathologically. The neurologic picture gave evidence of epidural lymphogranulomatous masses involving some of the spinal roots and part of the left brachial plexus. On the last admission the cerebral signs of lymphogranulomatous invasion over-

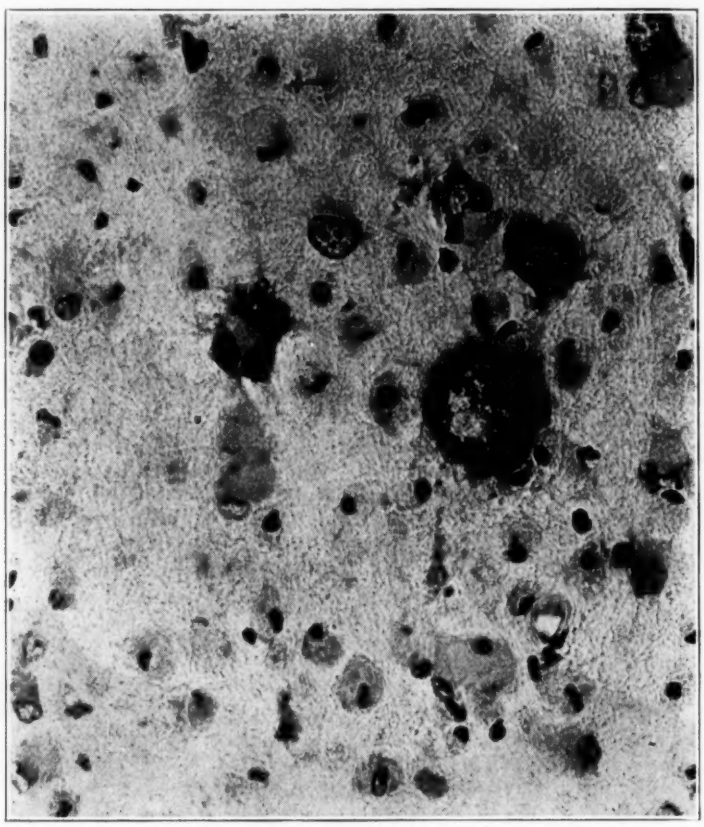

Fig. 5.—Higher power view of the section shown in figure 4. Plainly discernible are the gitter cells, the gemästete glia and the Sternberg-Reed cells, two of which are multinuclear and one uninuclear. Toluidine blue stain; × 450.

shadowed the evidence of involvement of the spinal cord. Involvement of both cerebral hemispheres was shown clinically by weakness of the right facial nerve of central type, turning of the head and eyes to the right, complete left hemiparesis, exaggerated tendon reflexes bilaterally, a bilateral Hoffmann sign, Babinski sign and ankle clonus, all more pronounced on the left, generalized twitchings over the entire body and, finally, unconsciousness.

The pathologic lesions corroborated the bilaterality of the cerebral symptoms. The brunt of the degenerative change was borne by the right cerebral hemisphere. Although the spinal cord was not available for study, there can be no question, from the similarity both to cases in the literature and to case 2 reported here, that the spinal roots were involved by epidural lymphograulomatous masses. Moreover, the clear-cut clinical evidence of involvement of the left brachial plexus can leave no doubt of its invasion by a Hodgkin process. The histopathologic studies showed the characteristic cellular components of Hodgkin's tissue in the dura and cerebrum, with the diagnostic Sternberg-Reed cells present in both.

CASE 2.—M. B., a woman aged 39, was admitted to the hospital on Sept. 1, 1931, complaining of paralysis of both legs and incontinence of the bowel and bladder of five days' duration.

She had been well until two years previously, when she began to feel weak, lost weight and acquired a productive cough. Swelling of the axillary glands was noticed at this time. In April 1929 biopsy of the cervical glands revealed Hodgkin's disease. She received roentgen therapy and showed a gain in weight and general improvement. In October 1930 roentgen therapy was stopped. Three weeks previous to the present admission to the hospital she noticed weakness and stiffness of the legs, and five days before admission the symptoms stated as her chief complaints developed.

On admission, the patient was emaciated and showed considerable enlargement of the left anterior and posterior cervical glands, which were hard and discrete and varied from the size of a pea to that of a large marble. Both supraclavicular chains were palpable. The chest revealed evidence of a pulmonary pathologic condition. The abdomen was distended and tense. The liver and spleen were not palpable. The axillary and inguinal glands were enlarged and hard.

Laboratory examination showed secondary anemia, and the colloidal gold curve of the spinal fluid was 2455543222.

A roentgenogram of the lungs revealed typical Hodgkin's disease. A roentgenogram of the spine showed destruction of the fourth lumbar vertebra, due to metastatic Hodgkin's disease.

The neurologic examination on Sept. 4, 1931 showed an almost complete transverse lesion of the cord, with complete flaccid paralysis of both lower extremities. The tendon reflexes were diminished or absent. Sensory tests showed loss of vibration sense, beginning at the sixth dorsal dermatome, loss of touch to the eighth dorsal dermatome, analgesia at the tenth dorsal dermatome and loss of sense of position in both legs. The patient died Sept. 13, 1931.

Gross Examination of the Central Nervous System.—An epidural mass was observed within the spinal canal adherent to the dura, mainly on the right side, at the level of the middle thoracic region of the cord. It measured 5 cm. in length, 1.5 cm. in width and less than 1 cm. in thickness. The outer surface was irregular and appeared to be made up of fused individual masses, which apparently had extended through the intervertebral foramens.

Cross section through the spinal cord at the level of the sixth thoracic segment showed softening of the substance of the cord but no actual necrosis. The brain showed no gross lesions.

Microscopic Examination.—The mass noted on gross examination was closely adherent to and infiltrated the outer surface of the dura, in places reaching its under surface, so that it formed a thin band in the subdural space (fig. 6*A*). The subarachnoid space was not invaded.

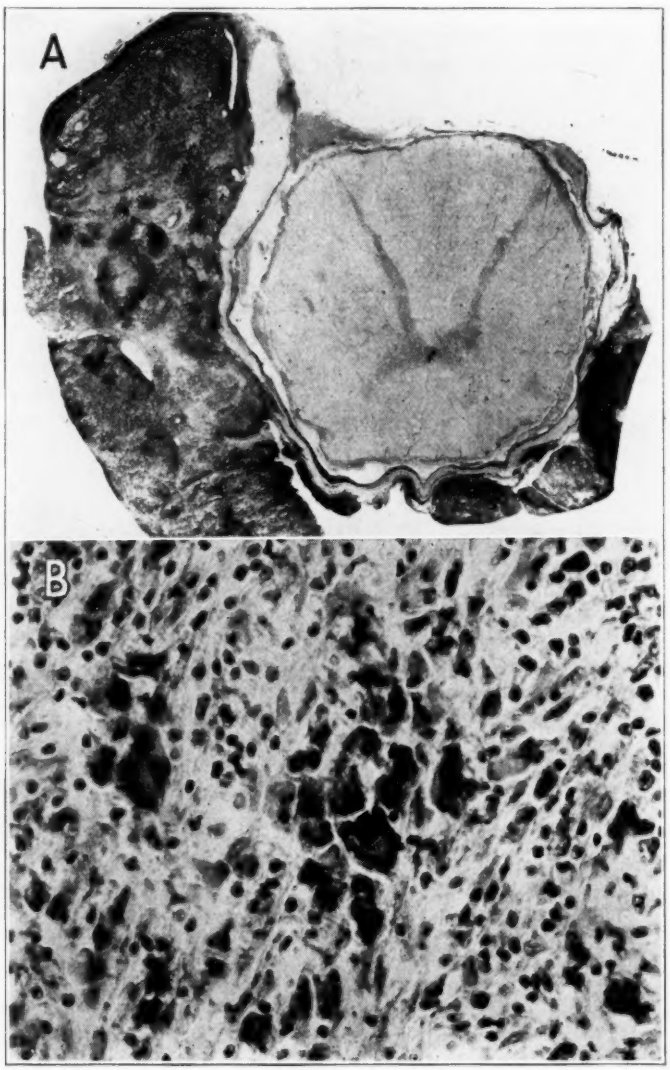

Fig. 6.—*A*, transverse section of the thoracic portion of the cord (case 2), showing epidural masses of lymphogranulomatous tissue. Rarefaction of the cord is seen by the *Lücken* distributed throughout the section. Toluidine blue stain; × 6. *B*, cellular picture of the lymphogranulomatous tissue illustrated in *A*, showing the characteristic lymphoid cells, epithelioid cells, connective tissue stroma and Sternberg-Reed cells. Toluidine blue stain; × 400.

The makeup of the mass was that of a typical lymphogranuloma (fig. 6*B*). There was a definite reticulum in which lay a great variety of cells grouped in masses, separated by coarse bundles of connective tissue. These cells were mainly endothelial, plasma, lymphocytes and endothelial giant cells, and many had multilobed hyperchromatic nuclei (Sternberg-Reed cells). Only an occasional area of necrosis was to be seen.

The spinal cord itself at the level of the lesion maintained its normal outline and anatomic configuration. The gray matter was distinct but showed loss of cellular structure and increase in glia. The white tracts showed loss of myelin sheaths and vacuolation (status spongiosus) without marked compensatory gliosis and with only a feeble effort at vascularization. There were some phagocytic elements within the white tracts, which were brought out clearly by fat stains. The axons were decreased in number, with secondary changes in those remaining, especially in the tracts showing wallerian degeneration.

From the clinical standpoint this case represents a classic picture of Hodgkin's disease. The first evidence of involvement of the spinal cord manifested itself about two years after the onset of the disease. The symptoms came on rapidly and consisted of weakness and stiffness of the lower limbs, followed by signs of a progressive transverse lesion of the cord. The roentgenographic finding of destruction of the fourth lumbar vertebra, due to metastatic Hodgkin's disease, bore no relation to the clinical neurologic findings, which were at a higher level.

The presence of an epidural lesion in the thoracic region explains the clinical neurologic aspects fully. Microscopically, the lesion was a typical lymphogranuloma. The spinal cord was degenerated secondarily as the result of pressure rather than of direct extension.

A general survey of 16 consecutive cases studied clinically and pathologically confirmed the impression gained from the literature that the more thoroughly cases of Hodgkin's disease are studied the greater the likelihood of finding signs and symptoms referable to the nervous system.

Of these 16 cases reviewed, in 10, or 62.5 per cent, there were signs and symptoms of implication of the nervous system. There were, in order of their frequency, lancinating pains, involving the limbs or torso, headaches, disturbances in gait, paralysis (mainly in the lower limbs), anesthesias, paresthesias, urinary incontinence, frequency of micturition, diplopia, photophobia, vertigo and mental changes. Symptoms referable to the spinal roots predominated. If the patient survived there was a strong possibility that epidural lesions and direct pressure on spinal roots, plexuses and peripheral nerves would be found to account for the more common neurologic signs and symptoms.

COMMENT

For many years investigators have called attention to the invasion of the nervous system by a lymphogranulomatous process, yet there have been only a few reports, with histopathologic study, of instances similar

to our first case. This case represents an unusual direct invasion of the brain substance without anatomic connection with a dural infiltration over the cerebral hemispheres. From the clinical manifestations it was evident that the left brachial plexus and the spinal epidural space were also involved.

Our second case is an example of the most common localization of Hodgkin's tissue within the central nervous system, namely, the spinal epidural space. In this case also the vertebrae were involved without anatomic relation to the lesion.

Weil,[4] in a review of 43 cases recorded in the literature and 3 cases observed personally, found epidural lymphogranulomatous masses in the spinal canal in 85 per cent. In an additional 7 per cent, in which paraplegia had been present and in which roentgen therapy had been given, only scar tissue in the spinal canal, indicating previously existing lymphogranulomatous masses, was present.

Allen and Mercer [5] reviewed the various methods by which spinal symptoms were produced by "lymphadenomatous tissue" and claimed that the commonest was epidural masses of Hodgkin's tissue without invasion of the vertebrae.

Case 1 represents many unusual aspects and some common neuropathologic features. Invasion of the cerebral dura is not unknown. Rizzi [6d] reported a case in which a large dural lymphogranulomatous mass compressed the left cerebral hemisphere and produced focal neurologic signs. The brain showed perivascular infiltration of lymphogranulomatous tissue cells along the pial vessels extending directly from the dural focus. The brain, however, did not show the picture reported in our case 1. Askanazy [7] reported a case in which the brain showed leptomeningitis, petechial hemorrhages and perivascular cellular cuffing; the cord presented an epidural lymphogranulomatous plaque at the fifth cervical segment.

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4. Weil, A.: Spinal Cord Changes in Lymphogranulomatosis, Arch. Neurol. & Psychiat. **26**:1009 (Nov.) 1931.

5. Allen, M., and Mercer, J. O.: Spinal Symptoms with Lymphadenoma, J. Neurol. & Psychopath. **17**:1 (July) 1936.

6. (*a*) Cooper, E. L.: Hodgkin's Disease: Some Clinical Aspects with Special Reference to the Effects upon the Hemapoietic Tissues and the Nervous System, M. J. Australia **1**:585 (May 11) 1935. (*b*) Stewart, H. H.: Hodgkin's Disease with Spinal Cord Involvement, Ulster M. J. **7**:68 (Jan.) 1938. (*c*) Keschner, M.: A Case of Hodgkin's Disease with Compression of the Spinal Cord Following Trauma to the Back, J. Mt. Sinai Hosp. **5**:301 (Nov.-Dec.) 1938. (*d*) Rizzi, I.: Il granuloma maligno del sistema nervoso, Riv. di neurol. **11**:377 (Oct.) 1938.

7. Askanazy, M.: Lymphogranulom des Knochenmarks, Verhandl. d. deutsch. path. Gesellsch. **24**:78, 1921.

There could be no doubt from the clinical aspects in case 1 that the spinal epidural space and related spinal roots, as well as the left brachial plexus, were invaded by lymphogranulomatous tissue. Signs and symptoms of such involvement have been noted by Ginsburg,[1] Weil,[4] Allen and Mercer,[5] East and Lightwood,[8] Delius [9] and many others.

The uncommon feature of our first case was the extensive invasion of the brain by lymphogranulomatous elements and the concomitant cerebral reaction. The nature and extent of the invasion would seem to indicate a hematogenous origin rather than an extension from the contiguous invaded dura.

Hecker and Fischer [10] described a case in which epileptiform seizures and coma preceded death. The brain showed small foci of degeneration (about the size of a cherry) symmetrically placed in the centrum ovale at the head of the nucleus caudatus on both sides. The sections showed perivascular cellular elements composed of lymphocytes, lymphoblasts and plasma cells. There were rare foci of Sternberg-Reed cells. They regarded the foci as blood-borne metastases.

Serebrjanik [11] reported a case which, in its clinical and neuropathologic aspects, most closely resembled our case 1. His patient, a man aged 40, had been ill for three and a half years. The neurologic signs came on six months prior to death and consisted of pains in the legs, headache, vomiting, ptosis of the left eyelid, diplopia and disturbances in movements of the eyes. Then followed bilateral weakness of the sixth nerve, evidence of compression of the spinal cord and meningeal signs. The spinal fluid showed pleocytosis and a meningeal type of colloidal gold curve. Mental symptoms came on shortly before death. In his case Serebrjanik noted numerous small lymphogranulomatous foci in the pons, corpus striatum and white matter of the cerebrum and a large focus near the corpus striatum. The cortex showed a lesser degree of involvement. He stated that the perivascular cellular cuffing was characteristic. There were numerous Sternberg-Reed cells. Transitional types occurred, varying from cells of lymphocytic form to giant cells. There was proliferation of astrocytes and rod cells. The pia contained lymphogranulomatous tissue. Serebrjanik expressed the belief that the "virus" of lymphogranulomatosis was transported to the brain by the hematogenous route.

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8. East, C. F. T., and Lightwood, R. C.: Compression Paraplegia in Lymphadenoma, Lancet **2**:807 (Oct. 15) 1927.

9. Delius, L.: Rückenmarkskompression durch Lymphogranulomatöse, Deutsche Ztschr. f. Nervenh. **125**:142, 1932.

10. von Hecker, H., and Fischer, W.: Zur Kenntnis der Lymphogranulomatöse, Deutsche med. Wchnschr. **48**:482 (April 14); 520 (April 21) 1922.

11. Serebrjanik, B.: Lymphogranulomatöse Meningo-Encephalitis und Polyradiculitis, Deutsche Ztschr. f. Nervenh. **129**:103, 1933.

Schöpe [12] reported a case of a 46 year old imbecile who had an "undifferentiated psychosis" and chorea. Grossly, a tumorous mass was observed in the left parietal area. Microscopically, the entire left hemisphere was seen to be invaded by cellular elements which were typically lymphogranulomatous. The right hemisphere was uninvolved.

A review of the literature would indicate that the involvement of the central nervous system is in the main the result of direct extension from adjacent Hodgkin's nodules. Penetration through the intervertebral foramens or direct extension from involved vertebral structures to the spinal epidural space explains in the majority of cases the signs and symptoms referable to the spinal cord. The infrequent cases of cerebral lymphogranulomatous invasion reported in the literature can be divided into two groups, those whose original focus is in the dura with secondary extension into the brain tissue and those with primary or separate intracerebral foci. From the study of our case 1, in which there was widely distributed discrete and confluent involvement of both cerebral hemispheres, and of similar cases in the literature, we agree with Serebrjanik,[11] who advanced the theory that such lesions must be blood borne.

The cellular constituents of the cerebral lesions differ in no great way from those seen in Hodgkin's lesions elsewhere in the body. There are obviously minor differences, depending on the basic structure of the invaded tissue. The cerebral lesions in our case were unquestionably lymphogranulomatous, with the presence of the pathognomonic Sternberg-Reed cells as conclusive.

Cerebral signs and symptoms during the course of recognized Hodgkin's disease should call to one's attention the possibility of intracranial invasion. When cerebral signs and symptoms precede the corporal manifestations of Hodgkin's disease, the diagnosis can be only speculative. However, it would be well to keep in mind Ginsburg's statement:

> . . . A review of the literature and my own cases have shown that the nervous system may become clinically, primarily and predominantly affected and give rise to symptoms for months and years before the occurrence of any demonstrable enlargement of the lymph nodes or spleen.

This is well exemplified by our first case, in which neurologic symptoms and signs were present for one year prior to the appearance of palpable lymph nodes or spleen.

SUMMARY

Two cases of Hodgkin's disease with involvement of the nervous system have been reported in detail. In case 1 there was clinical evidence of involvement of the brain, left brachial plexus and spinal epidural

12. Schöpe, M.: Zur Frage "Blastom"—"Encephalitis," Arch. f. Psychiat. **109**:755, 1939.

space. Histologic examination of the brain showed extensive intracerebral lymphogranulomatous foci and dural plaques.

In case 2 clinical and pathologic evidence of invasion of the midthoracic spinal epidural space by a Hodgkin's process was presented.

The histopathologic picture in both cases was typically that of Hodgkin's lymphogranuloma. The distribution and character of the cerebral lesions indicated a blood-borne invasion. Our cases, as well as those in the literature, point to the necessity for careful neurologic study in all cases of Hodgkin's disease, in view of the frequency with which the nervous system is involved.

ABSTRACT OF DISCUSSION

Dr. Charles Davison, New York: I can corroborate the statement of Dr. Winkelman and Dr. Moore with reference to the metastases to the central nervous system via the blood stream. I saw 2 cases of lymphogranulomatosis with similar metastases and a pathologic process in the cortex and white matter analogous to that shown by the authors. Metastases via the blood stream are more frequent in cases of myelogenous leukemia.

In most cases of lymphogranulomatosis the metastases are by direct extension, especially to the spinal cord. Direct invasion rarely takes place, and the myelopathy is usually due to compression of the vessels by the extradural neoplasm. As is well known, these tumors are highly radiosensitive. When the patients have been subjected to high voltage roentgen therapy, it frequently is impossible at autopsy to see the extradural tumor, although the myelopathic changes can be seen. I have seen 7 to 10 cases of lymphogranulomatosis with extradural metastases to the spinal cord.

Dr. Arthur Weil, Chicago: Had roentgen radiation been applied, and what had been the effect on the extradural granulation?

Dr. N. W. Winkelman, Philadelphia: Roentgen radiation had been applied to the extradural granulation, and there were evidences in the lesion of the effect of therapy. Fibrosis was present, without degenerative manifestations. Proliferative changes, however, were in the ascendency. The dural granuloma showed Sternberg-Reed cells of rather large size.

Dr. L. S. King, Princeton, N. J.: I believe the virus theory of Hodgkin's disease, especially as brought forward by Gordon, has been pretty well given up. I cannot understand how Hodgkin's disease could properly take root in the nerve tissue, where there is absence of reticulum cells and other fixed mesenchymal elements that give rise to the condition in lymph nodes. In the brain reported on, there were no evidences of circumscribed metastases of foreign tissue, such as are so familiar with metastatic carcinoma. Can Dr. Winkelman throw any light on the relation of the typical Hodgkin lesions elsewhere and the lesions in the brain?

Dr. N. W. Winkelman, Philadelphia: I, too, am of the opinion that the theory of the virus origin of Hodgkin's disease has been abandoned by most investigators. The question raised about the ability of the Hodgkin lesion to take root in the nerve tissue can be answered in this way: Metastatic lesions in Hodgkin's disease occur throughout the body. The mechanism of the metastasis is still in need of explanation. One can, however, visualize the cellular elements being transported through blood or lymphatic channels, rather than

whole portions of the granuloma. This mechanism is probably similar to that which occurs in cases of carcinoma and infectious emboli of subacute bacterial endocarditis.

Eckel and I have reported isolated, unattached cancer cells within the blood stream of the brain. The proliferation of these cells can take place in such a way that they bear no resemblance to the parent tumor. The absence of connective tissue within the intracerebral metastasis is the result of the dearth of connective tissue within the brain, except that in the vessel walls. For that reason it is not difficult to visualize a lesion that differs from the original source, just as melanotic tumors on reaching the brain are frequently completely devoid of pigment.

AN ADAPTATION OF THE SAYRE APPARATUS FOR USE IN ENCEPHALOGRAPHY

ESTHER H. READ, B.A.
BOSTON

A satisfactory method for supporting the patient during the performance of an encephalographic examination is necessary for its complete success; a single chair, even though adjustable, has not proved

Photograph showing the Sayre apparatus adjusted for the encephalographic procedure.

entirely satisfactory, in my experience, for the procedure in children. I have met this problem in the past year by adapting standard orthopedic apparatus to my own ends.

The Sayre head piece, commonly in use for head traction, is slipped onto the patient after he has been anesthetized. He is raised to sit cross legged, tailor fashion, on the table, his arms resting over a number of small pillows placed in his lap. The loops of the head piece are slipped

over the horns of the steel spreader, which hangs by a double pulley from a ring in the ceiling beam. The assistant extends the head by tightening the rope to the desired degree of tension, then fastens the rope to a cleat on the table. The patient can now be maintained in good position without further effort. He is stable but not rigid. There is a good airway, and the anesthetist need not divide her attention between the anesthesia and the support of the patient. The position can be easily altered if desired before the end of the procedure.

If the encephalographic procedure is to be done through the cisternal route, the Sayre apparatus is put on more loosely so that the pad at the occiput comes higher up on the head. The operator then has an unobstructed field and can be assured that the position of the head will not suddenly shift while his needle is in the cistern.

The leather extension is standard equipment, obtainable from the surgical supply houses for about $7. The pulley and spreader can be put up by the hospital maintenance department in an hour's time and at negligible expense.

Case Reports

INFARCTION OF THE BRAIN WITH UNILATERAL CIRCULATORY CHANGES

COBB PILCHER, M.D.; THOMAS E. WYATT, M.D., AND HENRY M. CARNEY, M.D., NASHVILLE, TENN.

Recently, 2 striking cases of extreme unilateral vasomotor disturbance associated with cerebral lesions have been reported. In the first, reported by Bucy,[1] there developed sudden right hemiplegia and hemianesthesia and aphasia, with absence of the radial pulse and unobtainable blood pressure in the right arm, thirteen days after a mild injury to the head. The right radial pulse first became palpable four hours after the cerebral accident. The blood pressure was first definitely obtained on the right side four days later and remained lower than that on the left for two additional days. The skin was "colder" on the right side for three days after the cerebral accident. All neurologic symptoms rapidly disappeared, and recovery was complete.

The second case was reported by Kerr and Underwood.[2] After acute right hemiplegia with motor aphasia ten years prior to examination, there developed coldness of the right extremities, variable weakness or absence of the right radial pulse, diminished sweating on the right side and jacksonian convulsions, beginning in the right upper extremity. Examination by the authors revealed that all arterial pulsations were diminished or absent and that the blood pressure was unobtainable on the right side. Encephalograms showed dilatation of the left lateral ventricle, with slight displacement to the left and indications of cortical atrophy on the left. The nature and extent of the lesion were unknown.

Pertinent prior reports were summarized by the authors already cited. Since their publications, Euzière, Lafon, Fassio and Payan [3] have reported 5 cases of jacksonian epilepsy, in 2 of which a lesion of the frontal lobe was proved to exist. The extremities on both sides were studied with the oscillometer, and in all cases oscillations on the affected side were found to be greatly diminished as compared with those on the normal side.

Read before the Harvey Cushing Society, Kansas City, May 2, 1940.

From the Department of Surgery, Vanderbilt University School of Medicine.

1. Bucy, P. C.: Vasomotor Changes Associated with Paralysis of Cerebral Origin, Arch. Neurol. & Psychiat. **33**:30 (Jan.) 1935.

2. Kerr, W. J., and Underwood, F. J.: Hemiconstriction of the Vascular System Associated with Cerebral Disease, Am. Heart J. **12**:713, 1936.

3. Euzière, J.; Lafon, R.; Fassio, E., and Payan: Les asymétries vasculaires périphériques dans les syndromes de la frontale ascendante, Arch. Soc. d. sc. méd. et biol. de Montpellier **19**:313, 1938. Euzière, J.; Lafon, R., and Fassio, E.: Méningiome pariétal gauche et crises Bravais-Jacksoniennes par irritation frontale contro-latérale, ibid. **19**:311, 1938.

Paulian, Bistricéanu and Fortunescu [4] studied 22 cases of hemiplegia due to hemorrhage, softening or tumor. Individual cases were not cited, and the exact locations of the lesions were not mentioned. However, the authors stated that unilateral autonomic phenomena occur only when the lesion involves or is "in the vicinity of" the pyramidal tract.

In contrast to the variable and incomplete clinical data available, experimental evidence has indicated the strong probability of extensive autonomic representation in the cerebral cortex. This field of research has been ably reviewed by Fulton,[5] Kennard,[6] Bucy [1] and Brickner.[7]

REPORT OF CASE

History.—H. C., a white American workman aged 45, was admitted to the medical service of Dr. W. D. Strayhorn on April 28, 1938.

In 1924 he had a "heat stroke," and subsequently whenever he became overheated he suffered cramping pains in all extremities, sometimes with vomiting. His right foot felt cold and remained so for many years. Six years before admission the right leg became weaker than the left, and three years later he noticed the same symptoms in the right arm and hand. At times he had numbness and tingling in the right extremities.

One year before admission he suddenly lost consciousness for thirty minutes but had no residual paralysis, anesthesia, aphasia or convulsions. Subsequently, he became forgetful, suspicious and worried. After several months he began to have difficulty in saying what he wished and was unable to perform simple arithmetical computations.

Examination.—Significant findings were confined to the circulatory and nervous systems.

The heart was not enlarged. There was no arrhythmia, thrills or murmurs. On the left side all arterial pulsations were full and bounding. In all the arteries on the right side the pulsations were greatly diminished, and at times impalpable. The blood pressure in the left arm was 208 mm. of mercury systolic and 100 mm. diastolic and in the right arm 144 mm. systolic and 90 mm. diastolic. In the left thigh it was 220 mm. systolic and 120 mm. diastolic. In the right thigh it could not be obtained.

There was no edema, cyanosis or trophic abnormality. On palpation, the skin was equally moist and warm on the two sides.

The patient was moderately confused. Speech was hesitant and thick. Simple mathematical calculations were poorly done.

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4. Paulian, D.; Bistricéanu, J., and Fortunescu, C.: Les asymétries de la tension artérielle et des différents réflexes neuro-végétatifs au cours des hémiplégies, Arch. de neurol. **3**:68, 1939.

5. Fulton, J. F.: The Interrelation of Cerebrum and Cerebellum in the Regulation of Somatic and Autonomic Functions, Medicine **15**:247, 1936; Cerebral Regulation of Autonomic Function, Proc. Interstate Post-Grad. M. Assemb. North America, 1936, p. 149.

6. Kennard, M. A.: Vasomotor Representation in the Cerebral Cortex, Science **79**:348, 1934.

7. Brickner, R. M.: Certain Characteristics of the Cortical Influence over the Sympathetic Nervous System in Man, J. Nerv. & Ment. Dis. **71**:689, 1930.

The pupils were equal, but reacted sluggishly to light. The remaining cranial nerves were normal. There was slight right hemiparesis, without spasticity or alteration of reflexes. No change in sensation was demonstrable. Coordination was good on both sides.

The urine and blood showed no abnormality. The cerebrospinal fluid pressure was 150 mm. of water. The cell count and protein content were normal, and the Wassermann reaction was negative.

Roentgenograms of the skull showed no abnormality.

Course.—Two days after admission right hemiplegia and motor aphasia suddenly developed. On the right were increased reflexes, a Babinski sign and ankle clonus, but no spasticity, Hoffman sign or reflex grasping. The blood pressure in the left arm was 220 mm. systolic and 120 mm. diastolic and in the right arm 94 mm. systolic and 80 mm. diastolic.

During the succeeding three days, the blood pressure in the right arm remained approximately the same and that in the left was usually about 40 mm. lower. The body temperature rose to 101 F. and remained at about that level. The pulse rate rose to and remained approximately 120 beats per minute. The patient remained drowsy and apathetic and was incontinent of urine. He sweated profusely on the right and little on the left. The right side was cooler than the left. Arterial pulsations on the right were feeble or impalpable. The right pupil was slightly larger than the left. Spasticity developed rapidly in the right arm and leg.

Various additional examinations were carried out, the results of which will be presented later.

Ventriculographic Examination.—On May 4 a ventricular cannula was inserted first into the left frontal lobe, but the ventricle was not encountered. The procedure was repeated on the right side and the ventricle entered at once. The ventricular fluid was under moderately increased pressure, and 30 cc. was replaced with air. Ventriculograms disclosed slight displacement of the right lateral ventricle and the third ventricle to the right. The third ventricle slanted to the right. The left lateral ventricle was not visualized.

Operation (May 6 1938).—Left cerebral craniotomy with disclosure of cerebral infarction.

With the patient under anesthesia induced by avertin with amylene hydrate supplemented by local anesthesia, a large osteoplastic flap was reflected. When the dura was opened, an extraordinary picture appeared (fig. 1). The following is quoted from the operative note.

"At the anteroinferior border of the exposed area the sylvian vessels could be seen emerging from the cleft and appeared to be normal. About 2 cm. within the flap they suddenly disappeared in a short area of thickened pia-arachnoid, which had a grayish yellow appearance, apparently representing complete obliteration of the vessels. Just anterior to this point a large distended vessel coursed toward the midline in almost a straight line. Posterior to the point of obliteration the sylvian vessels appeared to be constricted, if not occluded. The central sulcus could be distinctly identified, and the rolandic vessels were definitely thrombosed. In a roughly rectangular area extending a distance of two convolutions anterior to the central sulcus, inferiorly to the sylvian vessels, posteriorly to the second postcentral sulcus and medially to an irregular line just medial to the longitudinal fissure there was complete dead white pallor. The entire pale area was exceedingly soft, but the temporal lobe had a normal firmness on palpation. A ventricular needle inserted into the pale area met no resistance whatever, the feeling being almost as though it was passing through a liquid.

"A cellophane map was made of the cortex (fig. 2) and electrical exploration carried out. There was no response from any part of the exposed cortex. The pulse in the right arm, observed throughout the series of stimulations, showed no appreciable effect. Respiratory movements were unchanged.

"On account of the possibility of an underlying tumor suggested by the ventriculograms, an incision was made in the infarcted cortex posterior to the central sulcus. The cerebral tissue was dead white and completely necrotic. A con-

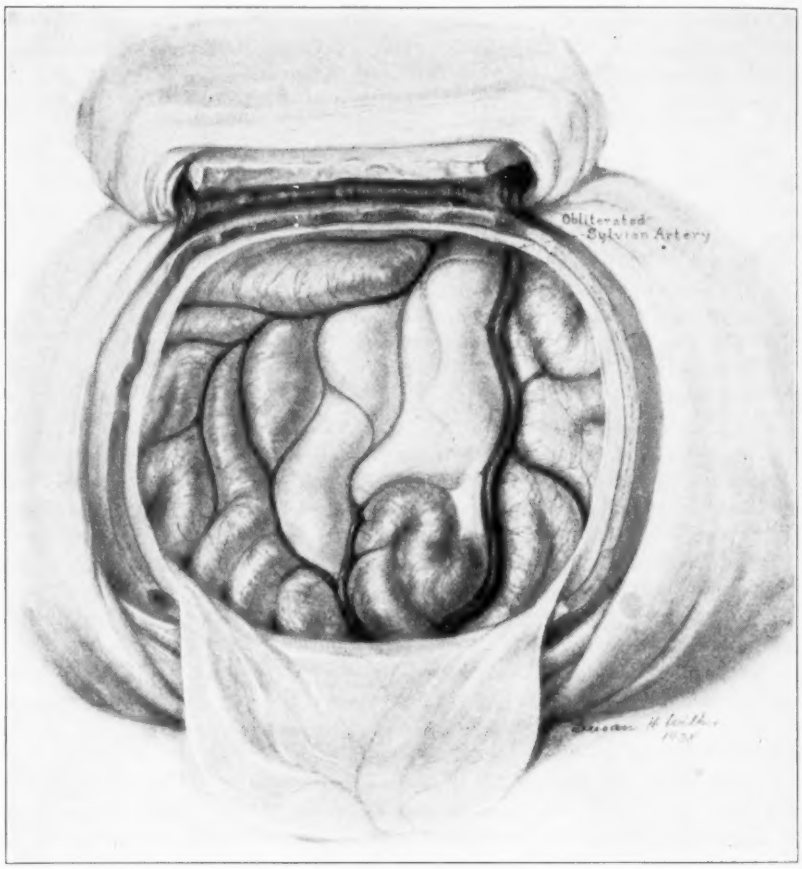

Fig. 1.—Drawing of operative field made at the time of operation. The area of infarction is clearly shown. The central sulcus lies in the center of the pale area.

siderable amount of it was removed with the sucker and with cup-jawed forceps. A frozen section showed a necrotic, almost homogeneous mass, in which numerous poorly formed astrocytes could be seen. There was no evidence of tumor. Before the bone flap was turned, the blood pressure in the left arm rose from its preoperative level of 140 systolic and 80 diastolic to one of 180 systolic and 100 diastolic, and this level was maintained, with minor variations, throughout the operation."

Postoperative Course.—Eighteen hours later, hyperpyrexia (maximum temperature, 106 F.) and evidence of bronchopneumonia developed, and the patient died thirty-two hours after operation. The blood pressure fluctuated greatly in both arms, as shown in the accompanying tabulation.

	Left Arm	Right Arm
Maximum	238 systolic, 110 diastolic	130 systolic, 100 diastolic
Minimum	120 systolic, 80 diastolic	Unobtainable at times

There was no significant change in the neurologic signs except that pilomotor activity was several times observed on the right and not on the left.

In spite of every effort, permission for postmortem examination could not be obtained.

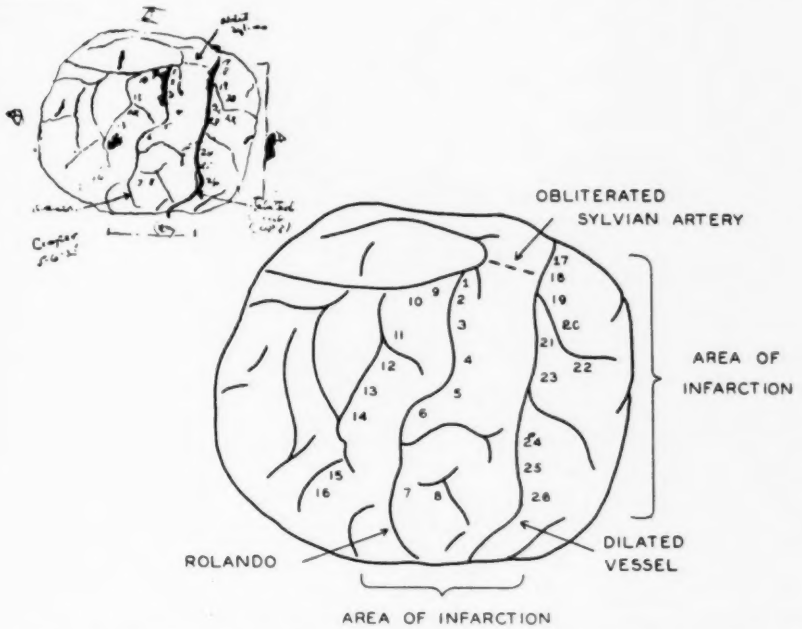

Fig. 2.—Tracing of the cortical map made on cellophane at operation. A photograph of the original map is shown in the inset. The numbers represent stimulated points. Compare with figure 1.

Preoperative Observations on Autonomic Functions.—Vasomotor Function: Resting blood pressure and arterial pulsations. These factors have already been discussed. They varied greatly, but the marked difference between the two sides was always present.

Vasomotor Function: Oscillometric readings. In both the left arm and the left leg oscillometric readings were from 0 to 2.0. In the right arm the readings were from 0 to 0.2, and in the right leg the oscillations were only barely perceptible and could not be measured.

Vasomotor Function: Resting cutaneous and deep temperature. Cutaneous temperature was determined with the Tycos "dermotherm" thermocouple and deep temperature with a portable galvanometer thermocouple, the needle of which was

thrust to a depth of 1.5 cm. into the end of the great toe. Temperature readings are shown in figure 3. The temperatures of the skin and deep tissues were consistently higher on the left than on the right, except in the hands.

Vasomotor Function: Tourniquet test. The test was employed essentially as described by Brooks and Jostes.[8] Circulation to each lower extremity was obstructed by an Esmarch bandage placed around the upper part of the thigh and left in position for fifteen minutes. Deep tissue temperature in the great toe was recorded every thirty seconds and cutaneous temperatures of the thighs, legs and feet at intervals of one minute. Deep temperature findings are plotted graphically in figure 4. The striking delay in return to the preexisting temperature after removal of the tourniquet on the right side is apparent.

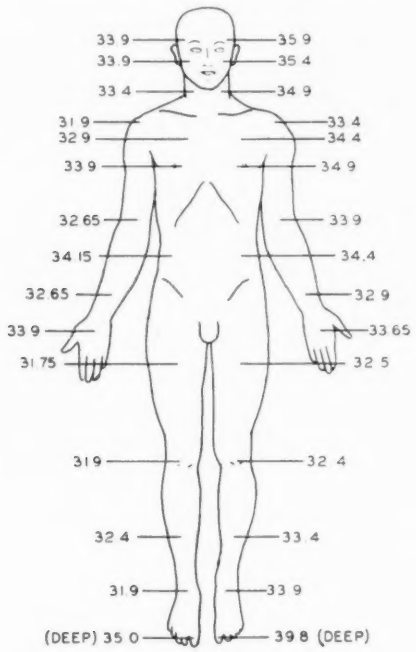

Fig. 3.—Diagram showing cutaneous and deep temperature readings, expressed in degrees centigrade. The room temperature was 80 F.; the body temperature, 38.3 C. (100.9 F.).

The changes in cutaneous temperature were much less marked and were essentially the same, in both degree and time, in the two legs.

When the tourniquet was removed from the left leg, immediate flushing of the leg and foot was observed. This was very faint after four minutes and completely absent after seven minutes. On the right, similar flushing appeared gradually two minutes after removal of the tourniquet and did not disappear until ten minutes later.

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8. Brooks, B., and Jostes, F. A.: A Clinical Study of Diseases of the Circulation of the Extremities: A Description of a New Method of Examination, Arch. Surg. **9**:485 (Nov., pt. 1) 1924.

Vasomotor Function: Effect of spinal anesthesia. The cutaneous temperature was determined after induction of spinal anesthesia. There was definite elevation of the temperature of the skin of both lower extremities, but that of the upper extremities showed a comparable elevation. Since the body temperature was actually falling at the time, no explanation can be given for this finding.

Sweating: As already stated, profuse sweating on the right side, with a sharp line of demarcation at the midline, was frequently observed.

Edema: No peripheral edema was observed on either side at any time, nor was there alteration in the circumference of the extremities.

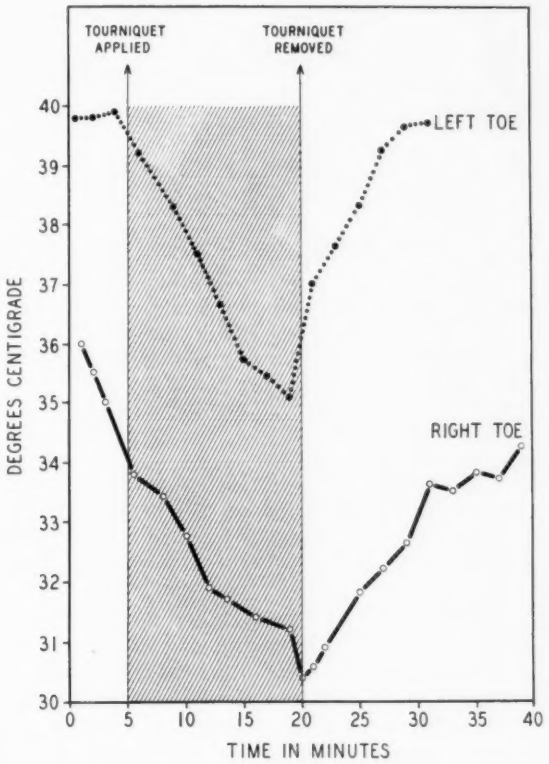


Fig. 4.—Plotted readings for deep temperatures observed in the tourniquet test.

Pilomotor Activity: Visible erection of hair was observed on the right side on several occasions. It was not accompanied by shivering.

Salivary Secretion: When Stensen's duct was held open on each side with a fine probe and secretion stimulated by lemon juice placed on the tongue, only a single tiny droplet of very viscid saliva was obtained on the right, whereas a succession of droplets of thinner saliva appeared on the left.

Intestinal Movements: The patient had only one spontaneous bowel movement while in the hospital, but enemas resulted in the elimination of normal-appearing feces.

A barium meal was given. The stomach and the upper portion of the small intestine showed normal peristalsis. A small five hour retention was found in the stomach. At the end of twenty-four hours the entire meal was in the ascending and transverse colon.

Oxygen Content of Venous Blood: [9] Samples of blood were drawn in duplicate under oil from the antecubital vein of each arm and from both femoral veins, without the use of a tourniquet in any instance. Values for oxygen content, expressed in volumes per cent, follow.

Left Arm	Right Arm	Left Femoral Vein	Right Femoral Vein
11.7	19.3	10.6	18.8
10.8	19.0	11.3	19.3

Pupils: The pupils were round and regular and were equal except on one occasion, when the right was slightly larger than the left. Consensual reaction was normal, but the direct reaction to light was sluggish in both eyes on all occasions.

Bladder: The patient voided involuntarily at intervals of two to four hours. There was no dribbling and no retention of urine. Polyuria and polydipsia were not present.

Genital Symptoms: No priapism or other abnormality of the genitalia was observed.

Electrocardiograms: Curves made from four leads were interpreted as follows: "The character of the S-T interval in the fourth lead is compatible with but not diagnostic of myocardial disease, and the character of the P waves may be due to auricular rather than to sinus tachycardia."

COMMENT

As in the cases of Bucy [1] and of Kerr and Underwood,[2] the circulatory phenomena observed in this case can be explained only as the results of an extreme degree of unilateral vasoconstriction. This explanation is strongly supported by the other evidences of sympathetic overactivity which were present.

The general location and nature of the cerebral lesion in this case were demonstrated at operation, but its exact extent cannot be stated. Certainly, subcortical structures were involved to a considerable depth. It is likely that the sylvian artery was occluded just anterior to the origin of its prerolandic branch (operative note). The areas supplied by the more posterior branches were presumably saved from complete necrosis by collateral circulation, though the probable presence of hemianopia indicates their involvement. That the deeper branches were involved is indicated by the completeness of the hemiplegia and the aphasia (Foix and Lévy,[10] Bailey [11]).

9. Dr. Max Little did the gas analyses of the blood, which were made on the Van Slyke-Neill constant volume manometric apparatus.

10. Foix, C., and Lévy, M.: Les ramollissements sylviens: Syndromes des lésions en foyer du territoire de l'artère sylvienne et de ses branches, Rev. neurol. **2**:1, 1927.

11. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933, pp. 58-60.

Regardless of these factors, the most significant fact is that the lesion seen at operation must have been confined to the cortical and subcortical portions of the cerebral hemisphere and could not have involved the vegetative nuclei in the hypothalamus. The observations recorded therefore constitute strong presumptive evidence of the existence of extensive autonomic representation above the level of the hypothalamus in man. Such evidence is in accord with the extensive experimental and meager clinical observations already cited.

The neurologic mechanism of the autonomic phenomena observed must remain a matter of speculation at present. A priori, since the lesion was a destructive one, it seems likely that many of the changes resulted from overactivity of lower sympathetic neurons "released" from higher (e. g., cortical) inhibition.

A finding of great interest in this case is the higher oxygen content of the venous blood on the affected side. It is believed that this observation may be of considerable importance, but conclusions are not justifiable on the basis of a single case. Further clinical and experimental observations on the subject are in progress and will be reported elsewhere.

SUMMARY

A case is reported of a patient who was found at operation to have extensive cerebral infarction involving all or a major portion of the distribution of the left middle cerebral artery.

This patient presented, in addition to spastic right hemiplegia, absence or great diminution of the pulsations of all the major arteries on the right side. The blood pressure was either unobtainable or greatly lowered on the right side.

Observations on various autonomic functions gave evidence of unilateral overactivity of the sympathetic nervous system.

The findings in the case are compatible with extensive autonomic representation in the cerebral cortex.

Obituaries

THIERRY DE MARTEL, M.D.
1876-1940

To his many friends in this country it was a profound shock to learn of the death by suicide of Dr. de Martel on the day the German army entered Paris, June 14, 1940. He was well known in the United States as he had been a frequent visitor here and spoke English readily. He was likewise chief surgeon to the American Hospital at Neuilly, Paris, and had performed an appendectomy on the former Helen Wills in 1926.

Thierry de Martel de Janville was of distinguished French lineage. He was the son of the Countess de Martel and was born on March 7, 1876, at Maxéville (Meurthe-et-Moselle). His mother, under the pseudonym of "Gyp," wrote numerous witty and satiric sketches, and through her he was descended from Mirabeau. He was similarly proud of his descent from that Martel who was the "Hammer of the Saracens."

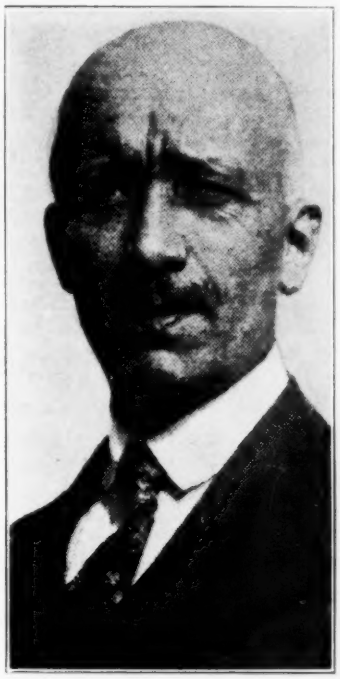
De Martel was a brilliant student of medicine and took his doctor's degree in 1907, with a thesis entitled "The Immediate Treatment of Hemorrhage in Wounds of the Lung." He became in the same year chief of the surgical clinic of the faculty in the service of Dr. Segond at the Salpêtrière. Almost from the beginning of his surgical career he developed an interest in neurosurgery and, through Clovis Vincent and other pupils of Babinski, began to do Babinski's neurosurgical work, thus becoming the pioneer in this field in France. This was about 1909.

Across the channel, in England, Sir Victor Horsley had already laid the foundations of this newest surgical specialty, and de Martel, either on his own initiative or at the instigation of Babinski, made frequent trips to London to see Horsley operate. He had himself, however, made several contributions to neurosurgery even at this early era, among them the invention of a trephine with which the skull could be opened without damage to the dura and brain.

In 1914, during the first world war, de Martel was severely wounded but after recovering he was actively engaged in operating on the wounded. In 1918 he wrote, with Dr. Charles Chatelin, a book on the "Treatment of Gunshot Wounds of the Brain" (Paris, Masson & Cie.). He received the cross of the Legion of Honor in 1914 and the rosette in 1919. He was also decorated with the Croix de Guerre. After the war he made several visits to this country, particularly to see Dr. Harvey Cushing and to learn more about neurosurgical methods from this master.

Dr. de Martel was an ingenious operator and an independent thinker. He removed the second tumor of the spinal cord ever extirpated successfully in France, and of course had many enucleations of brain tumors to his credit. His own published works covered a large range of subjects both in general surgery and in neurosurgery. He also translated, in 1924, Dr. Cushing's epoch-making monograph on "Tumors of the Nervus Acusticus."

Perhaps the two things for which de Martel was most famous from the neurosurgical standpoint were his advocacy of local anesthesia and



THIERRY DE MARTEL, M.D.
1876-1940

the employment of the sitting posture in cranial operations. In both of these innovations he was the pioneer, and both have proved their worth, even though all neurosurgeons do not use these measures as consistently as he did. He was the first French surgeon to divide the sensory root for trigeminal neuralgia and probably the first there to do a chordotomy.

As Clovis Vincent said recently of de Martel, he did all he could to make himself acquainted with the neurosurgery of his time. He and Vincent were closely associated in their earlier days, but later, to the sorrow of their friends, they became estranged. However, as Vincent

beautifully put it: "What does it matter that our different conceptions of neurosurgery separated us. . . It remains true that in the history of French neurosurgery, the name of de Martel rests beside that of Babinski, and my name with that of de Martel."

The German occupation of the French capital was apparently too much for a man of de Martel's intense patriotic spirit, and he ended his life by an injection of strychnine. According to the *New York Times* (July 17, 1940), he left the following message to United States Ambassador William C. Bullitt: "If I stay in Paris it is like putting a signed check in the enemy's hands. If I stay in Paris dead, it is a check without funds. . . Adieu."

News and Comment

THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

The following certificates were issued at the meeting of the board at New York on Dec. 18 and 19, 1940.

Neurology.—By examination: * Crawford N. Baganz, Lyons, N. J.; * Richard F. Binzley, Brentwood, N. Y.; * Hollis E. Clow, White Plains, N. Y.; * Benjamin Cohen, North Grafton, Mass.; * William Corwin, Waltham, Mass.; * Anna R. Coyne, Washington, D. C.; * Arthur Manning Doyle, Kingston, Ontario, Canada; Adolph Eisenbud, New York; Edward M. Gould, New York; John M. Radzinski, Chicago; * Conrad O. Ranger, Norwich, Conn.; James L. Sagebiel, Dayton, Ohio; * Isidore Schnap, Kings Park, N. Y.

Psychiatry.—By examination: Lewis Barbato, Galveston, Texas; William Calvin Barger, New York; Harvey Bartle Jr., Philadelphia; Florence A. Beaulieu, Palmer, Mass.; Thomas W. Brockbank, New York; Louise A. Brush, New York; Julia Deming, Boston; * Harold Lloyd Ellis, New York; J. Louis Philippe Forest, Waterbury, Vt.; Robert E. Gardner, Catonsville, Md.; Walter P. Gardner, Anoka, Minn.; Joseph J. Gitt, St. Louis; Louis Henry Gold, Hartford, Conn.; Julius R. Haight, Wingdale, N. Y.; Dorothy Harpham, New York; Arthur Orr Hecker, Harrisburg, Pa.; James M. Henninger, Pittsburgh; Helen LaRue Williams Hodgens, Philadelphia; Salvador Jacobs, Hathorne, Mass.; William J. Johnson, Lowell, Mass.; Otto Kant, Worcester, Mass.; Samuel C. Karlan, Dannemora, N. Y.; Attilio Laguardia, Orangeburg, N. Y.; Zigmond M. Lebensohn, Washington, D. C.; Joseph Lerner, Ann Arbor, Mich.; Ernest George Lion, San Francisco; Earl W. Mericle, Philadelphia; Grant E. Metcalfe, South Bend, Ind.; Charles W. Miller, Medical Lake, Wash.; Leo Patrick O'Donnell, Brentwood, N. Y.; Lauchlen S. Palmer, Brentwood, N. Y.; Luis Perelman, New York; George N. Raines, Philadelphia; Bernard S. Robbins, New York; Theodore Robie, East Orange, N. J.; Benjamin Ruskin, Wauwatosa, Wis.; * Nathan S. Schlezinger, Philadelphia; Kathryn L. Schultz, Albany, N. Y.; Ulysses Schutzer, Binghamton, N. Y.; Louis A. Schwartz, Detroit; Rudolph Schwarz, Dannemora, N. Y.; * John T. Shea, Foxboro, Mass.; Herman Shlionsky, Cedar Grove, N. J.; Norman R. Shulack, Brooklyn; * Samuel E. Soltz, New York; William G. Srodes, Woodville, Pa.; Alfred M. Stanley, Orangeburg, N. Y.; George C. Stevens, Indianapolis; Abraham M. Stiffle, Taunton, Mass.; Simon Stone, Manchester, N. H.; Daniel J. Sullivan, Asheville, N. C.; Frank W. Tallman, Orangeburg, N. Y.; Victor Hugh Vogel, Washington, D. C.; James N. Williams, Richmond, Va.; Lyle Lynden Woodfin, Kansas City, Mo.; Bascom B. Young, Wingdale, N. Y., and William G. Young, Hartford, Conn.

On record: Edwin W. Allen, Milledgeville, Ga.; Sydney G. Biddle, Philadelphia; Morris Braude, Chicago; Roy E. Bushong, Columbus, Ohio; Samuel A. Butler, Pontiac, Mich.; Earl H. Campbell, Newberry, Mich.; Hugh S. Gregory, Queens Village, N. Y.; G. Leonard Harrington, Kansas City, Mo.; Louis P. Harshman, Fort Wayne, Ind.; James C. Hassall, Oconomowoc, Wis.; Powell L. Hays, Vinita, Okla.; Clarence M. Hincks, Toronto, Canada; Emmett L. Hooper,

* Denotes complementary certification.

Dayton, Ohio; William N. Keller, Fort Steilacoom, Wash.; Roy H. Long, Morgantown, N. C.; Berry C. Marshall, Baltimore; Ward W. Millias, Rome, N. Y.; George W. T. Mills, Queens Village, N. Y.; Thomas V. Moore, Washington, D. C.; Augusta Scott, New York; George W. Smeltz, Pittsburgh; Neville E. Stewart, Northport, N. Y.

Neurology and Psychiatry.—By examination: S. Muriel Baron, New York; Clemens Ernst Benda, Wrentham, Mass.; Newton J. T. Bigelow, Brentwood, N. Y.; S. Stephen Bohn, Detroit; Henry Brill, Brentwood, N. Y.; Samuel C. Burchell, New York; Theodore J. Case, Chicago; Hervey M. Cleckley, Augusta, Ga.; Charles Davison, New York; Harold H. Dodds, Marcy, N. Y.; Howard D. Fabing, Cincinnati; David J. Flicker, Kearny, N. J.; Richard V. Foster, Brentwood, N. Y.; Israel S. Freiman, New York; Emerick Friedman, Norwich, Conn.; Sherman F. Gilpin Jr., Philadelphia; Lionel M. Ives, Westwood, Mass.; Morris M. Kessler, Cleveland; Walter O. Klingman, New York; John Galloway Lynn, New York; Wilbur R. Miller, Iowa City; Mary E. O'Sullivan, New York; Fredy Albert Quadfasel, Brooklyn; John Romano, Boston; Abraham L. Schwartz, State Farm, Mass.; Carmine T. Vicale, New York; Karl O. Von Hagen, Los Angeles; Paul S. Wolfe, Worcester, Mass.; Herman Wortis, New York, and David A. Young, Waverley, Mass.

On record: Larue D. Carter, Indianapolis; John G. Cullins, American Lake, Wash.; John M. Dunsmore, St. Joseph, Mo.; Horace J. Forman Jr., Washington, D. C.; Otto G. Freyermuth, San Francisco; Josef Gerstmann, Washington, D. C.; Manfred L. Gorten, Newark, N. J.; Moses Keschner, New York; Joshua H. Leiner, New York; John G. Lloyd, Pittsburgh; L. Vosburgh Lyons, New York; William Mayer, Amityville, N. Y.; Theodore W. Neumann, Central Valley, N. Y.; Cleve C. Odom, Corozal, Canal Zone; Hale Powers, Wellesley, Mass.; George H. Reeve, Cleveland; Paul Louis Schroeder, Chicago; Francis M. Shockley, Stamford, Conn.; Harrison A. Wigton, Omaha; Harry J. Worthing, Brentwood, N. Y., and George A. Young, Omaha.

OPPORTUNITIES FOR FELLOWSHIPS

A limited number of fellowships have been provided by the Commonwealth Fund and other sources of training in extramural, especially child, psychiatry. These fellowships are to be administered by the National Committee for Mental Hygiene, through whom fellows are to be assigned for one or two years to a selected child guidance clinic, the term and plan of the fellowship to be determined by the peculiar needs of the fellows. Candidates for fellowship award should have at least two years of psychiatry in an approved mental disease hospital, in addition to other qualities fitting them for extramural service. These fellowships come in response to a definite paucity of personnel in this field. Accordingly, other conditions, such as those relating to age, sex and marital status, must be governed by individual needs and by the nature of current demand. Requests for further information about these fellowships, and applications therefor, should be addressed to Dr. Milton E. Kirkpatrick, the National Committee for Mental Hygiene, Room 916, 1790 Broadway, New York.

Abstracts from Current Literature

Physiology and Biochemistry

LIPID METABOLISM IN BRAIN AND OTHER TISSUES OF THE RAT. W. M. SPERRY, H. WAELSCH and V. A. STOYANOFF, J. Biol. Chem. **135**:281, 1940.

Sperry, Waelsch and Stoyanoff determined the distribution of labeled fatty acids in the brain, liver, intestine and remaining carcass of adult rats at varying intervals (from eight to forty-eight hours) after the administration of a single small amount of deuterium-containing fat. Only traces of the labeled fatty acids were found in the brain. The largest concentrations were observed in the liver and intestine. Although the concentration was small, a large but variable proportion of the total amount given was found in the depot (carcass) fatty acids. The variation bore no evident relation to the time after administration. The authors call attention to constitutional variation in the amount of fat in the stores as a factor to be considered in interpreting studies of fat metabolism.

PAGE, Indianapolis.

A STUDY OF THE SYNTHESIS AND DEPOSITION OF LIPIDS IN BRAIN AND OTHER TISSUES WITH DEUTERIUM AS AN INDICATOR. H. WAELSCH, W. M. SPERRY and V. A. STOYANOFF, J. Biol. Chem. **135**:291, 1940.

Waelsch, Sperry and Stoyanoff determined the concentration of deuterium in the unsaponifiable and fatty acid fractions of the brain, liver, intestine and carcass of adult male rats after periods of four to seven days, during which the body fluids were enriched with deuterium through the administration of heavy water. In the unsaponifiable fraction of the brain, the concentration of deuterium was little above the possible error of the method, while all other tissues contained large concentrations. It is concluded, therefore, that the lipids comprising this fraction are replaced at a very slow rate. The concentration of deuterium in the fatty acid fraction of the brain, on the other hand, was comparable with that found in the depot (carcass) fatty acids, and it was estimated that as much as one fifth of the fatty acids of the brain may be replaced in a week. In the fatty acids of the liver the concentration of deuterium was higher than in any other tissue. The concentration of deuterium in the unsaponifiable fraction of the liver was less on the average than that of the carcass and no greater than that of the intestine. Thus the liver does not appear to have the same dominant role in the metabolism of unsaponifiable substances as it does in the metabolism of fatty acids. Relatively large concentrations of deuterium in both the unsaponifiable and the fatty acid fraction of the intestine direct attention to this organ as an active participant in endogenous lipid metabolism.

PAGE, Indianapolis.

LIPID METABOLISM IN BRAIN DURING MYELINATION. H. WAELSCH, W. M. SPERRY and V. A. STOYANOFF, J. Biol. Chem. **135**:297, 1940.

Waelsch, Sperry and Stoyanoff investigated the deposition of lipids in the rat brain during myelination with the aid of deuterium as an indicator. Unsaponifiable lipids and fatty acids are deposited at a rapid rate from the fifteenth to the nineteenth day of extrauterine life. The rate is considerably less from the twenty-sixth to the thirtieth day, and still lower from the thirty-sixth to the fortieth day. If allowance is made for turnover comparable with that found in adult rats, no marked differences in the rates of deposition of the unsaponifiable and of the fatty acid fraction are evident. The data indicate that lipids deposited between

the fifteenth and the nineteenth day of life are synthesized in the brain itself. The relationships of rates of lipid metabolism in the liver, intestine and remaining carcass were in general the same as were found in adult rats, but in most instances the deuterium uptake was considerably higher in the young than in the adult rats. Determinations on mother rats agreed closely on most points with those in adult male rats.

PAGE, Indianapolis.

OCULAR MOVEMENTS FROM THE OCCIPITAL LOBE IN THE MONKEY. A. EARL WALKER and THOMAS A. WEAVER JR., J. Neurophysiol. **3**:353 (July) 1940.

Contralateral conjugate deviation of the eyes with lateral or with either upward or downward components was obtained by stimulation of the occipital cortex. When the exciting electrodes were applied to the cortex of area 17 superior to the calcarine fissure the movements tended to be lateral and downward; when they were applied below the same landmarks the deviations were lateral and upward.

ALPERS, Philadelphia.

INTERCORTICAL CONNECTIONS OF CORPUS CALLOSUM AS INDICATED BY EVOKED POTENTIALS. HOWARD J. CURTIS, J. Neurophysiol. **3**:407 (Sept.) 1940.

In monkeys and cats under barbiturate anesthesia, single electric shocks were applied to the cortex of one hemisphere and the other cortex was explored for evoked potentials. The only regions not studied were those which cannot readily be exposed by removal of the calvarium. In general, the stimulus evokes potentials in one or more specific areas on the other cortex. The magnitude of the response is quite variable; it may be several millivolts. In general, the waves are diphasic and sometimes have a duration as long as 100 milliseconds.

The largest and most readily detected potentials are those obtained when the stimulating and recording electrodes are placed on symmetrically situated points of the two cortices. In the cats studied all regions yielded potentials from symmetric contralateral stimulation. With the exception of the operculum of the occipital lobe (area 17), the same was true of the monkeys. Localized stimulation within certain areas may evoke potentials over a considerable portion of the corresponding contralateral area; conditions of these experiments are mediated by direct callosal fibers, and evoked potentials are sharply localized. They are fairly reproducible from animal to animal.

These effects are completely abolished by section of the corpus callosum.

ALPERS, Philadelphia.

THE INFLUENCE OF ALCOHOL ON THE ADEQUACY OF THE B VITAMINS IN THE AMERICAN DIET. NORMAN JOLLIFFE, Quart. J. Studies on Alcohol **1**:74 (June) 1940.

It has been pointed out that alcohol addicts who consume little food are subject to the so-called alcoholic diseases, whereas those who eat well and in whom assimilation is not impaired seldom acquire these diseases. The factors furnished by alcohol that increase the prevalence of nutritional deficiency diseases in addicts are primarily four: the irritant action on the gastric mucosa; the interference with absorption and utilization of vitamins; the substitution of vitamin-free alcohol for vitamin-containing food, and the increased vitamin requirement in consequence of the calories furnished by the alcohol. The role of alcohol in the production of vitamin deficiencies and its significance in influencing the margin of safety have been elaborated by using vitamin B_1 as an example of all the B vitamins. The American diet, already dangerously low in the B vitamins, is further significantly diminished by the average consumption of alcohol by the average American consuming an average diet.

ALPERS, Philadelphia.

AN EXPERIMENTAL STUDY OF THE ROLE OF NEURONES IN THE DISSEMINATION OF POLIOMYELITIS VIRUS IN THE NERVOUS SYSTEM. DAVID BODIAN and HOWARD A. HOWE, Brain **63**:135, 1940.

The fact that the distribution of observable lesions in the nervous system corresponds with the distribution of the poliomyelitis virus made it possible to use histologic methods to study the spread of the virus following experimental inoculation of monkeys. The animals were infected through different sites of inoculation, and were killed at varying intervals after injection. The course of spread of the virus was followed histologically. The following routes of spread of infection were determined: 1. After intranasal inoculation, the infection spreads through the olfactory bulb to the anterior perforate substance, the preoptic area and the hypothalamus and thence through the descending pathways (the olfactotegmental and hypothalamotegmental tracts and the periventricular bundle of Schütz) to the tegmentum of the midbrain and the reticular formation of the hindbrain. From the latter regions, the virus passes to the motor centers of the medulla oblongata and spinal cord, apparently by way of many short connections. In later stages "side chains" are infected, the parolfactory regions, the amygdaloid nuclei, and the midline gray matter of the dorsal thalamus being thus involved. If one olfactory tract is divided prior to infection, the spread is limited to the intact side as far back as the region of the midbrain, below which it crosses and later becomes bilateral. If both olfactory tracts are divided, the infection remains localized to the olfactory bulbs. 2. After inoculation of the motor cortex, the infection spreads through the corpus callosum to the opposite motor cortex and from both cortexes to the dorsal thalamus. From there the infection spreads by way of the tegmentum and the reticular formation to the spinal cord. From subcortical centers in the tegmentum of the midbrain and subthalamus the pathway from the olfactory bulb is invaded in a retrograde direction. 3. Inoculation of retrorolandic cortical areas produces infection only through spread to the motor cortex, the sensory and optic cortex being relatively resistant to infection. 4. Inoculation of prerolandic cortical areas results in rapid dissemination of the virus to the motor cortex, and thence to the pathway with which it connects. At the same time, the infection involves the pathway ordinarily infected by the intranasal route, and in addition the insula, the claustrum, the septal nuclei and the nucleus medialis dorsalis of the thalamus, all of which have connections with the frontal cortex. 5. After intraocular inoculation, the virus spreads through the ciliary ganglion and the oculomotor nerve to the midbrain. From there it spreads caudally and rostrally along the primary pathways involved following infection by the intranasal or the motor cortical route. 6. After infection by the sciatic nerve, skin, peritoneal cavity or spinal canal, the area of involvement is similar to that seen after intranasal infection. However, infection from below fails to involve the olfactory bulbs, the olfactory centers and the midline nuclei of the thalamus. Examination of these structures in cases of infection in man will reveal whether the infection was intranasal or gastrointestinal or whether it entered by some other portal.

Bodian and Howe conclude that the virus of poliomyelitis travels through the central nervous system along certain preferential pathways, determined by (*a*) differential susceptibility of certain centers, (*b*) accessibility of the virus as determined by the kind and quantity of neuronal connections between any center and other centers from which the virus can spread, and (*c*) portal of entry.

In the early stages of the disease the distribution and the severity of the lesions depend chiefly on the site of inoculation. In the later stages the virus usually involves all of the preferential areas, and, in addition, invades susceptible centers not included among those primarily affected, with the result that the final picture is similar, with slight differences, regardless of the portal of entry.

The evidence indicates that the virus spreads along neuronal pathways and is conducted most rapidly over short chains, where the perikarya serve to increase the concentration of the infecting agent.

MASLAND, Philadelphia.

Neuropathology

ACUTE LYMPHOCYTIC CHORIOMENINGITIS: REPORT OF THREE CASES WITH HISTOPATHOLOGIC FINDINGS. W. L. SILCOTT and KARL NEUBUERGER, Am. J. M. Sc. **200**:253 (Aug.) 1940.

In view of the scarcity of necropsy material on acute lymphocytic choriomeningitis, Silcott and Neubuerger report 3 cases, the first of a 72 year old white man, the second of a 67 year old white man and the third of a 79 year old white woman. The cases were characterized by acute onset with definite meningeal signs, including changes in the cerebrospinal fluid such as increased fluid and pleocytosis with lymphocytes predominating, a short course and favorable termination. It is believed that the virus isolated by Armstrong and Lillie in 1934 is the etiologic agent. The meningitic process was characterized by patchy lymphocytic infiltration of the leptomeninges, most marked in the neighborhood of the midbrain and pons. The patchy distribution and areas of predilection did not conform with any other known type of meningeal infection. The encephalitic process, chiefly perivenous, was of moderate intensity in all cases, and in distribution corresponded closely with the centers of predilection in epidemic encephalitis. The senile changes present were incidental and quite independent of the inflammatory changes.

MICHAELS, Boston.

HISTOLOGIC CHANGES FOLLOWING VASCULAR SPASM IN THE CENTRAL NERVOUS SYSTEM. A. J. NEDZEL, Arch. Path. **28**:697 (Nov.) 1939.

According to Nedzel, transient vascular spasms induced by injections of pitressin cause definite changes in the central nervous system which can be observed histologically. The early changes consist of swelling of the endothelium of the capillaries and the appearance of small hemorrhages. The leukocytes (mostly polymorphonuclear) increase in number; glia cells accumulate among the blood vessels, and the perivascular spaces and tissues around the blood vessels become edematous. Later, thrombotic blood vessels are observed, the thrombi being composed largely of fibrin, which later becomes hyalinized. In some of these thrombi leukocytes are engulfed. Swollen myelin sheaths and axons are observed in scattered patches. Gliosis is noted, and definite changes occur in the nerve cells, ranging from simple hydration to necrobiosis, manifested by the appearance of fat droplets and shrinking and twisting of the fibrils, to final neuronophagia. If the spasms are induced over a longer period there may be observed new changes, such as thickening of the walls of blood vessels, which does not result from mere swelling of endothelial cells, as in the initial changes, and the appearances of fibrous glia cells in greater numbers.

WINKELMAN, Philadelphia.

HISTOLOGIC SEQUENCES IN THE MENINGIOMA, WITH A CONSIDERATION OF THE NATURE OF HYPEROSTOSIS CRANII. ORVILLE T. BAILEY, Arch. Path. **30**:42 (July) 1940.

According to Bailey, the meningioma is a tumor arising from the arachnoid cell, either in the arachnoid villi or on the surface of the arachnoid. Neither the ectodermal theory of the French neuropathologists nor the fibroblastic theory of Mallory in regard to the origin of this tumor is considered by Bailey sufficient to explain completely the variations in histologic structure encountered in a series of these neoplasms.

The arachnoid cell is differentiated and is specialized as a covering cell. The differentiation persists in meningiomas, with the result that the neoplastic cells require a supporting and nutritive stroma. Consideration of the sequences of growth shows that the arachnoid cells retain their covering property in the tumors; they cover intercellular fibers, blood vessels or themselves, with the result that whorls are built up.

The stroma of meningiomas consists of several elements, the most constant of which are collagenous connective tissue and blood vessels. The fibroglia fibrils seen in meningiomas belong to the fibroblasts of the stroma and not to the neoplastic cells. Elastic tissue also forms part of the stroma of some meningiomas.

Hyperostosis cranii is produced by involvement of the skull by the meningioma. It develops when the stroma of the meningioma is derived from the periosteum. An ossifying stroma is then produced which gives rise to a mass of bony tissue with tumor cells in the interstices.

Bone plaques not connected with the periosteum occur occasionally in meningiomas. These plaques result from ossification of areas of degeneration in the tumors.

The great number of histologic variants of the meningioma depends on relationships of the neoplastic cells, with their tendency to cover whatever they touch, to a complex stroma, which continues to form intercellular materials similar to those which the component parts form under normal circumstances. The term "arachnoblastoma" is suggested by the writer for these tumors as more accurate than the term "meningioma," but the latter is convenient and familiar. The term, however, should be restricted to tumors arising from arachnoid cells and not extended to include neoplasms which have little in common with them except location.

WINKELMAN, Philadelphia.

EFFECTS OF AN ANTERIOR CALLOSAL GLIOBLASTOMA MULTIFORME ON THE ENTIRE BRAIN. MYRTELLE M. CANAVAN, Arch. Path. **30**:122 (July) 1940.

Canavan reports the case of a man aged 64 who was overcome by a rapidly growing tumor of the brain, which was recognized as of the corpus callosum and inoperable. The diagnosis was confirmed at autopsy. The tumor involved the anterior portion of the corpus callosum and adjacent white matter, particularly on the right side. Total sections were made from seven coronal slices of the cerebrum and one of cerebellum. They were stained by the original Weigert method for myelin sheaths. The tumor replaced brain tissue focally, distorted the hemispheres and increased the vascularity anterior to the tumor but did not destroy myelin peripheral to it. Microscopic examination of the neoplasm revealed a typical glioblastoma multiforme.

WINKELMAN, Philadelphia.

DISTRIBUTION OF AFFECTED NERVE CELLS IN AMYOTONIA CONGENITA. J. LEROY CONEL, Arch. Path. **30**:153 (July) 1940.

The brain, spinal cord and dorsal root ganglia of an infant 5½ months of age who presented clinical evidences of amyotonia congenita were removed at autopsy. Sections prepared from all parts of these structures were carefully examined for evidences of pathologic changes. Such evidences were found only in nerve cells and consisted of gradual degeneration of the cell body. The affected nerve cells were previously definitive normal cells, at least some of which had myelinated axons. The degeneration of the cell body was accompanied by a corresponding loss of myelin from the axons. In this case, as well as in another previously described by the author, affected cells were found among the Betz cells in the gyrus frontalis anterior, in the lateral nucleus of the thalamus, in the somatic efferent nuclei of the oculomotor, trochlear and abducens nerves, in the branchial (special visceral) efferent nuclei of the facial, glossopharyngeal, vagus and accessory nerves (nucleus ambiguus), in the lateral vestibular nucleus, in the somatic motor nucleus of the hypoglossal nerve, among the motor cells in the formatio reticularis and the nucleus supraspinalis, in Clarke's column, among the somatic efferent cells in the anterior column of gray matter in the spinal cord and in the dorsal root ganglia.

Affected neurons are reported here for the first time in the nucleus of the trochlear nerve, in the lateral vestibular (Deiters') nucleus and in the spinal ganglia.

WINKELMAN, Philadelphia.

MENINGIOMA. NATHAN CHANDLER FOOT, Arch. Path. **30**:198 (July) 1940.

Foot states that the meningioma appears to be a tumor of composite makeup, comprising two groups of cells: the meningocytes, derived from the arachnoid villi, and the stroma cells, coming from the mesenchymal elements of the pia-arachnoid. Usually the former predominate, and it is probable that they represent the type cell of the meningioma. The weight of experimental evidence is claimed to point toward derivation of these cells from the neural crests, and this view is reenforced by their dissimilarity to fibroblasts both in respect to their morphologic aspects and in respect to their staining reactions with acid fuchsin, ponceau de xylidine and orange G, for all of which they show an affinity not evidenced by fibroblasts. From the standpoint of their architecture they more closely resemble growths associated with neural than those associated with pure fibrous tissue. The importance of the presence of melanin in members of the same series should be stressed and a relationship between pigmented meningeal tumors and meningiomas tentatively advanced. The production of psammoma bodies, or corpora arenacea, has purposely been ignored in this paper, as they appear to be by-products which are normally seen in pacchionian bodies and may occur in other tumors, where they appear to be definitely subsidiary products. It is also to be noted that the malignant melanomas usually tend to have an epithelioid rather than a fusocellular sarcomatoid appearance such as might be expected from derivatives of fibroblasts.

WINKELMAN, Philadelphia.

CALCIFICATION OF SMALL VESSELS OF THE CEREBELLUM. HARRISON S. EVANS, ARNOLD P. FRIEDMAN and CYRIL B. COURVILLE, Bull. Los Angeles Neurol. **5**:18 (April) 1940.

Deposition of calcium in the pineal body and choroid plexus may be considered physiologic. Pathologically, calcification occurs in intracranial tumors, infectious granulomas, parasitic lesions, the walls of abscesses or hemorrhagic cavities and the walls of blood vessels. Calcification of the blood vessels in the cerebellum may be only part of a generalized cerebral arteriosclerosis, but more rarely it may be confined to the cerebellum. Evans, Friedman and Courville report 2 cases in which elderly men died soon after severe injuries to the head. One of the patients had preexisting Paget's disease and syphilis. In both cases pathologic study revealed medial calcification of the large arterioles of the cerebellum and profuse deposits of calcium in spherules about capillaries and smaller arterioles, which had been ultimately obliterated. In the first case, these changes were observed both in the centrum of the cerebellum and in the cortex, as well as in the blood vessels involved in an old focal vascular scar. In the other case, the calcification was observed predominantly in the cerebellar white matter and in the softened dentate nuclei. Cerebellar hemorrhage due to the fatal trauma had obviously been facilitated by the vascular disease in both cases.

In the opinion of Evans, Friedman and Courville, the deposit of calcium in the small vessels is the result of interference with tissue respiration, lowering of local concentration of carbon dioxide and the formation of insoluble calcium salts. Relative anoxemia may promote this process. The selective action on the cerebellum may possibly be dependent on excessive local arteriosclerosis and partial thrombosis, with consequent further interference with tissue respiration in this region.

MACKAY, Chicago.

PARALYSIS OF UPWARD GAZE (PARINAUD'S SYNDROME) ASSOCIATED WITH HEMIHYPERALGESIA. KARL O. VON HAGEN, Bull. Los Angeles Neurol. Soc. **5**:90 (April) 1940.

Von Hagen reports the case of a diabetic woman aged 58 who suddenly became dizzy and had blurred vision and pain in the right leg. Neurologic examination revealed sluggish, unequal pupils, paralysis of upward and impairment of downward gaze and slight diplopia. Tendon reflexes were absent in the lower

extremities, and there was hyperalgesia of the right leg. Later, slight weakness of the right side of the face was noted. The patient died ten months after the onset of the illness. Autopsy revealed generalized cortical atrophy, cerebral arteriosclerosis and a cystic vascular lesion, measuring 2 by 6 mm. in cross section, immediately dorsal to and slightly implicating the left red nucleus and extending upward into the medial nucleus of the thalamus. Since no other significant changes were noted, it appeared that the disturbance of conjugate upward and downward gaze was due to the mesencephalic portion of this lesion, which, though unilateral, must have involved commissural fibers of the mechanism for conjugate vertical movements of the eyes. The extension of the lesion into the left thalamus probably caused the pain and hyperalgesia of the right leg.

MACKAY, Chicago.

SIGNIFICANCE OF THE NATURE AND POSITION OF TUMORS OF THE BRAIN IN THE DEVELOPMENT OF CEREBRAL EDEMA. ALEXANDER BONKALO, Deutsche Ztschr. f. Nervenh. **149**:243, 1939.

Ninety-six intracranial tumors found at the Tönnis clinic were studied to determine the relation of the degree of malignancy and the location of the tumor to the degree of swelling of the brain. The material included the common tumor types in the ratio usually seen. The degree of swelling seemed directly related to the rate of growth; i. e., it was greatest in cases of glioblastoma and decreased in cases of metastatic malignant growth, astrocytoma and oligodendroglioma in that order. The swelling seemed to be greatest when the tumor was in the frontal lobe, less when it was in the parietal or occipital lobe and least when it was in the temporal lobe. Bonkalo distinguishes swelling and internal hydrocephalus; therefore one finds tumors of the brain stem low in the list, because of the early onset of internal hydrocephalus.

LOWIS, New York.

Meninges and Blood Vessels

CERTAIN FACTORS GOVERNING THE INCIDENCE OF CEREBRO-VASCULAR CRISES. DANIEL L. DOZZI, Am. J. M. Sc. **200**:259 (Aug.) 1940.

Dozzi analyzed the protocols of 1,000 consecutive autopsies to determine any particular factors which might govern the occurrence of cerebrovascular accidents. The brain was examined in 138 instances. In 116 (33.8 per cent) of the 343 cases of heart disease there was a complicating cerebral lesion, associated with hemorrhage and thrombosis in the majority of instances, whereas the incidence of cerebral lesions in the entire group of 1,000 cases was 16.7 per cent. Since hypertension was observed twice as frequently (in 52 per cent), and cerebrovascular accidents more than twice as frequently in association with cardiac disease, it is suggested that hypertension per se, rather than the cardiovascular disease proper was responsible for the cerebral lesions. There was auricular fibrillation in 4.3 per cent of the 1,000 cases and in 3.5 per cent of those in which cerebral lesions occurred. Of 524 cases, reactions for syphilis were positive in 79 and negative in 445. Syphilis was not an important etiologic factor in cerebrovascular accidents. There was a gradual, progressive incidence with advancing age, except for the younger group with associated rheumatic heart disease. Cerebrovascular lesions occur three times as frequently in females as in males, and nearly twice as often in white persons as in Negroes.

MICHAELS, Boston.

TRAUMATIC EXTRADURAL HAEMORRHAGE. A. RENDLE SHORT and MARJORIE DUNSTER, Brit. M. J. **1**:884 (June 1) 1940.

Traumatic extradural hemorrhage, characterized by a brief period of concussion, a lucid interval lasting a few minutes or hours and subsequent renewed unconsciousness with deepening signs of cerebral compression, has long been

known but is seldom seen. One of the authors saw only 1 case during a period of forty years. The authors describe a case of fatal traumatic extradural hemorrhage with a typical clinical picture of extradural hemorrhage. The bleeding originated from the superior longtiudinal sinus. In a second case the clot, which originated from a torn middle meningeal artery, was not removed until the nineteenth day after injury. The hematoma was accurately localized by an electroencephalogram.

ECHOLS, New Orleans.

CHRONIC MENINGOCOCCIC SEPTICEMIA ASSOCIATED WITH OUTBREAK OF CEREBROSPINAL FEVER. A. W. STOTT and W. S. C. COPEMAN, Lancet **1**:1116 (June 22) 1940.

Stott and Copeman state that chronic meningococcic septicemia is not well known in England. The meningococcus may inhabit the blood stream for weeks, months or even years and causes an illness which is so characteristic that it should be as readily recognized as meningococcic meningitis. Recent experience in France has led the authors to believe that chronic meningococcic septicemia is not uncommon but is often overlooked because of a superficial resemblance to other conditions. They present details in 17 of 27 cases of this type that they have encountered recently. Although the isolation of the meningococcus from the blood is the only certain method of diagnosis, chronic meningococcic septicemia is so characteristic that bedside diagnosis is simple. Early diagnosis is important, as grave complications may arise. Early diagnosis is also important because sulfapyridine is a prompt and effective remedy. The onset of the disease is usually sudden, with fever, chilly feelings or rigor, severe headache and severe migratory joint and muscle pains. Within a few days a characteristic rash appears. The lesions are usually pink or red macules, papules and nodules. The papules and nodules are sometimes painful. The rash is most profuse on the limbs and on the back of the trunk. Successive crops appear, often with the rise of temperature, and each crop lasts for a few days, leaving a slight brownish discoloration. If treatment with the sulfonamides is not given the fever persists for weeks, months or even years. It is either intermittent or irregular and relapsing. The rise of temperature may be accompanied by chilly feelings or rigor and a fresh crop of cutaneous lesions. The chief complications are meningitis and infective endocarditis; nephritis and acute epididymitis also occur. In 1 of the authors' cases acute epididymitis developed. This disappeared rapidly with sulfapyridine treatment; 1 patient had mild peripheral neuritis in the legs, with loss of ankle jerks and sensory disturbances, and a few complained of residual painful stiffness of muscles after all signs of active infection had disappeared. The history of 2 patients with cerebrospinal fever suggested chronic meningococcic septicemia for from two to four weeks before the onset of meningitis. Administration of sulfapyridine orally in moderate doses terminated the course of the disease within twenty-four hours in 15 cases. There was a rapid return to health. The authors' experience with the disease has led them to believe that this type of meningococcic infection is common whenever meningococcic meningitis becomes prevalent in a community. The cases recorded were seen within a period of nine weeks during the prevalence of cerebrospinal fever in the British Expeditionary Force.

J. A. M. A.

Diseases of the Brain

THE RELATIONSHIP OF MIGRAINE TO HYPERTENSION AND TO HYPERTENSION HEADACHES. JOHN W. GARDNER, GEORGE E. MOUNTAIN and EDGAR A. HINES JR., Am. J. M. Sc. **200**:50 (July) 1940.

Gardner, Mountain and Hines questioned 100 patients who had been seen because of hypertension concerning the presence of migraine or a previous history of migraine in an attempt to determine whether there is an association between

migraine and hypertension. The ages of the patients varied from 20 to 65, the majority falling between the ages of 40 and 60. There were 38 men and 62 women. Seventy-nine per cent of the patients who had hypertension were subject to migraine or had had such attacks in the past, as compared with an incidence of only 15 per cent in a control group consisting of 100 patients who had normal blood pressure and whose ages were between 40 and 60. During 1938, the diagnosis of migraine was recorded approximately five times as frequently in the group in which a diagnosis of hypertension was also recorded as in the group in which the diagnosis of hypertension was not recorded. Forty-four of 100 patients who had hypertension complained of a hypertensive type of headache. Of the 21 patients who had not had migraine, only 6 (28 per cent) experienced the development of of a hypertensive type of headache. Of the 79 patients who had associated migraine, 37 (46 per cent) gave a history of migraine in their respective families. Of the 21 patients who had no associated migraine, only 2 (10 per cent) gave a history of both migraine and hypertension. The incidence of migraine was approximately the same for both men and women. It is commented that a common factor in the pathogenesis of the two conditions is intimately connected with their close association, and it is suggested that this may be influenced by genetic factors which concern particularly the inheritance of a certain type of personality. The findings tend to indicate that of all persons with high blood pressure, those who previously had had migraine are more likely to experience a hypertensive type of headache as one symptom of the hypertension than those not so afflicted.

MICHAELS, Boston.

INSULIN AND CEREBRAL DAMAGE. F. KLEIN and J. A. LIGTERINK, Arch. Int. Med. **65:**1085 (June) 1940.

With the widespread use of insulin in the treatment of diabetes, and especially with its employment in the treatment of many types of mental illness during the past few years, various cases of serious, chronic disturbances of the brain have been reported. Observations on insulin shock therapy have shown that despite peroral or intravenous administration of dextrose full return of consciousness does not always occur within the time limits usually observed. Neurologic and mental symptoms are a frequent accompaniment of insulin shock therapy, and in some cases these may persist for weeks, months or even permanently. It is essential, therefore, to consider the possible danger to diabetic patients treated with protamine zinc insulin, for with this form of insulin the blood sugar can be kept at abnormally low levels for many hours.

The authors describe 2 cases of serious injury to the brain. In the first case, a patient of 25, suffering from schizophrenia, was treated by the method of Sakel. On the twenty-fifth day of treatment, despite oral and intravenous administration of dextrose, the patient failed to recover consciousness, although the blood sugar was raised to 224 mg. per hundred cubic centimeters. Neurologic and mental symptoms closely resembling those of severe encephalitis, were present to a marked degree. Seven months after the institution of treatment the intellectual status was found to be at the 8 year level.

The second case was that of a 22 year old man with diabetes, whose regimen included 25 units of protamine zinc insulin and 20 units of regular insulin daily. When found in a comatose state, he was given another 60 units of regular insulin. The coma persisted for six days, during which extensive neurologic disturbances, including convulsions, were observed. The intellectual level never returned beyond that of an idiot.

Danger to the brain ensuing from shock therapy induced by insulin, as well as from the treatment of diabetes, should not be underestimated.

BECK, Buffalo.

EXOPHTHALMOS, WITHOUT PULSATION, DUE TO ARTERIOVENOUS ANEURYSM. STIRLING S. MCNAIR, Arch. Ophth. **23**:22 (Jan.) 1940.

In cases of mild exophthalmos it is often difficult to be sure that true exophthalmos is present. The usual signs of pulsating exophthalmos consist of rapid development of signs, a bruit, rapidly failing vision and blindness; in the majority of cases there is a history of trauma. In the case reported by McNair, all the cardinal signs were present except pulsation, which is rarely absent with an aneurysm between the internal carotid artery and the cavernous sinus. The condition in the present case terminated in blindness, due to acute glaucoma and ulceration of the cornea, complete external ophthalmoplegia and complete peripheral paralysis of the facial nerve.

SPAETH, Philadelphia.

GLIOMA OF THE OPTIC NERVE. J. M. WILSON and W. D. FARMER, Arch. Ophth. **23**:605 (March) 1940.

In general, tumors of the optic nerve are divided into two large groups: (1) the dural endotheliomas or meningiomas, which arise from the fibrous sheath of the nerve, and (2) the gliomas, which arise from the neuroglial elements within the nerve itself. Clinically, the meningiomas seem to be more malignant than the gliomas, a fact recognized by Hudson in 1912; in fact, the differences between the late course of the meningiomas and that of the gliomas is outstanding. In the 29 cases cited by Hudson, 4 patients died of recurrences, while in only 1 of the various cases of glioma which have appeared in the literature was there any intracranial extension, and this only after nine years.

Wilson and Farmer report 2 cases: (1) that of a child aged 8, who died shortly after craniotomy for removal of the intracranial portion of the tumor, and (2) that of a child aged 3, who had uneventful enucleation of the tumor, which was wholly extracranial. In this case the tumor appeared in the eye, as well as in the optic disk.

The most important question is that of treatment. With reference to the meningiomas the answer is not difficult. These tumors tend to recur and to extend centrally; it would seem that the procedure of choice is craniotomy, followed if necessary by exenteration of the orbit. In the case of the glial tumors the problem is not as simple. The tumor does not tend to metastasize, even locally, but extends centrally by way of the nerve and is contained entirely within the sheath. Simple removal by the anterior approach to the orbit may be sufficient in most of cases of glial tumors. The authors advocate primary craniotomy in cases in which enlargement of the optic foramen is seen roentgenographically, to be followed by a second operation from the front for removal of the orbital portion of the tumor which remains.

SPAETH, Philadelphia.

THE UNSOLVED PROBLEMS IN APHASIA: III. AMNESIC APHASIA. J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **5**:78 (April) 1940.

The patient with amnesic aphasia is alert, cooperative and able to talk and explain that he "knows but can't say it." His concepts are clear, except for their verbal symbols, which he cannot recall. In some cases only nouns, in others verbs, are lacking. The words cannot be recalled spontaneously or after visual or tactile perception of the object, but can be recognized when heard or seen. In transcortical motor aphasia, on the other hand, the patient does not have a clear idea of the word he wishes, repeats indiscriminately any word offered him, has difficulty with all parts of speech and talks little. The location of the lesion evoking amnesic aphasia is in doubt, having been placed variously from the frontal to the posterior part of the temporal lobe. This type of aphasia unquestionably may arise from lesions of the posteroinferior portion of the major temporal lobe. It is found in some cases of lesion of the angular gyrus, but not in all. Nielsen briefly describes 7 cases from the literature which indicate that amnesic aphasia

may be due to lesions involving the supramarginal gyrus in the major parietal lobe. In all these cases, impingement on the posterior portion of the superior temporal convolution was immediate. In almost all cases there was disturbance also of writing and reading. Nielsen concludes that amnesic aphasia results from a lesion of the major posterior temporo-occipital region or its superior connection with the rest of the brain through the temporal isthmus—Brodmann's area 37 and the posterior portions of areas 21 and 22.

MACKAY, Chicago.

INTRACRANIAL CAUSES OF HEADACHE. HENRY COHEN, Brit. M. J. **2**:713 (Oct. 7) 1939.

Headaches are usually anatomically classified as intracranial, cranial, reflex, toxic, migraine or psychogenic. The site, duration, character and intensity of the headache will aid in locating the lesion responsible for this symptom. The author states that only a relatively small number of sufferers from chronic headache are victims of organic intracranial disease. Headache is a common symptom of tumor of the brain and cerebral edema, meningeal irritation and diseases of the cerebral arteries. It has been observed that the severity of headache increases with the rapidity of development of the causative pathologic lesion and with the definite interference with circulation of the cerebrospinal fluid.

Three varieties of headache are associated with intracranial disease: a dull or throbbing unilateral pain in the forehead, most often associated with expanding lesions of the brain; a sharp pain in the back of the head, usually seen in cases of subarachnoid hemorrhages and meningitis, and the migrainous type of headache commonest in vascular lesions.

Various explanations for headaches associated with expanding lesions have been offered. High and low cerebrospinal fluid pressure may be responsible for this type of headache. Excessive tension in the walls of the cerebral blood vessels has been considered a causative factor. The author believes that this type of headache is the result of cerebral anoxia.

In the cases of patients complaining chiefly of headache there should be a careful anamnesis and detailed clinical examination. If an intracranial lesion is suspected, lumbar puncture and encephalographic study should be undertaken. The author gives the following suggestions as an aid in diagnosing conditions responsible for headache. Headaches paroxysmal in character, increasing in severity and frequency and accompanied by dizziness, vomiting, mental deterioration, epileptiform attacks or signs of involvement of the facial nerve should suggest organic disease of the brain. Migraine beginning after the age of 40 may be indicative of gross intracranial disease, such as cerebral tumor, syphilis and hypertensive cerebral arteriosclerosis. Unilateral migrainous headache followed by ocular paresis is almost synonymous with the presence of basal intracranial aneurysms. Severe headache associated with recurring attacks of cyclic vomiting in children usually indicates a tumor of the posterior fossa. The diagnosis of psychogenic headache should be made only on the basis of positive evidence.

ECHOLS, New Orleans.

PARINAUD'S SYNDROME. P. VAN GEHUCHTEN, J. belge de neurol. et de psychiat. **40**:126 (March) 1940.

Van Gehuchten reports the pathologic observations in the case of a man aged 66 with Parinaud's syndrome. There was a sudden onset of tinnitus, followed by loss of consciousness and paralysis of all four extremities. The coma persisted for several days, and after regaining consciousness the patient had paralysis of the right side of the face and body, with pain in the right half of the face. The pupillary reflexes were normal, and visual acuity was good. Lateral and downward movements of the eyeballs could be performed normally; convergence was normal, but there was complete paralysis of upward gaze. The outstanding pathologic change was a hemorrhagic area in the midbrain at the base of the

third ventricle and surrounding the aqueduct, localized at the site of the nucleus of Darkschewitsch. Van Gehuchten concludes that the nucleus of Darkschewitsch is an important center for the production of vertical movements of the eyes.

DE JONG, Ann Arbor, Mich.

Diseases of the Spinal Cord

SYNDROME OF NEUROMYELITIS OPTICA. J. L. FETTERMAN and W. P. CHAMBERLAIN JR., Arch. Ophth. **23**:577 (March) 1940.

Fetterman and Chamberlain report a case of Devic's disease, or neuromyelitis optica. The condition is one of a vast group of nonsuppurative infections of the nervous system, which includes multiple sclerosis, Schilder's disease and acute disseminated encephalomyelitis. Many neuropathologists believe that these four conditions are one and the same, but with different manifestations. The case was that of a girl in the late teens who suffered from acute bilateral optic neuritis with acute myelitis. Blindness preceded the definite signs of involvement of the spinal cord, which was manifested by complete paralysis of both legs, loss of sphincter control and marked hyperesthesia of the legs and thighs. In the course of several months the patient regained completely the vision of the left eye and had only minimal impairment of vision in the right. There was almost total return of both sensory and motor functions.

The authors state: "Although there is an apparent striking difference between neuromyelitis optica and chronic multiple sclerosis, the distinction may be merely that of the time element rather than an actual difference in etiologic agent or the pathologic process. In neuromyelitis optica the changes occur simultaneously or consecutively in a matter of several weeks, while in multiple sclerosis these same structures may be affected in the course of years. One may think of the analogy of this relation to various forms of tuberculosis; there may be galloping tuberculosis, with an acute pulmonic involvement, and chronic fibroid phthisis. In one instance the process may be acute and last a few weeks; in the other instance the disease process may extend over a period of many years, though the causation of the two conditions is the same."

SPAETH, Philadelphia.

INFECTIOUS EQUINE ENCEPHALOMYELITIS IN THE UNITED STATES IN 1939. Pub. Health Rep. **55**:601 (April 5) 1940.

The incidence, mortality and distribution of equine encephalomyelitis in the United States reported for 1939 (8,008 cases) was only about 4 per cent of the number of cases (184,662) reported in 1938. There were 2,471 deaths from the disease. These figures give a case rate of 1.1 per thousand animals (horses and mules) in the affected counties and a case fatality rate of 30 per cent. The case fatality rate for the eastern type of virus was apparently more than three times that for the western type. In twenty-four states in which only the western type of the disease was proved or suspected the case fatality rate was 26.7 per cent, as compared with 89 per cent in nine states in which only the eastern type was proved or suspected. More than 90 per cent of the cases were reported to have occurred during the summer or early fall. This seasonal prevalence tends to support the prevailing conception regarding the principal natural means of transmission by blood-sucking insects, especially mosquitoes. The reported incidence of encephalomyelitis in vaccinated and unvaccinated horses and mules was 0.37 and 1.2, respectively, per thousand animals. No less than 3,000,000 horses and mules (about one fifth of the total in the United States) received specific prophylactic treatment. Vaccination and the retardation of insect breeding appear as the major factors in the control of the disease in animals and its transmission to man.

J. A. M. A.

COMBINED CHARCOT-MARIE-TOOTH AMYOTROPHY AND FRIEDREICH'S DISEASE IN SEVERAL MEMBERS OF A FAMILY. LUDO VAN BOGAERT and M. MOREAU, Encéphale **2**:312 (June) 1940.

Van Bogaert and Moreau describe the cases of an uncle and nephew with similar symptoms suggesting the combination of amyotrophy and Friedreich's disease. Of the mother's 5 children, 2 daughters were healthy and the third, the mother of the second patient, had dementia paralytica. The first son died at 33, with intense atrophy of the legs and bilateral "clubfoot." The second son, the authors' first patient, is now 40. He was unable to walk until 9 years of age. No progression of the disorder was apparent. Examination showed marked kyphoscoliosis, legs of the pipestem type, with atrophy extending into the thighs, and a high arch with dorsiflexion of the big toes. He could stand only on a wide base. The tendon reflexes were absent in the arms and legs; the abdominal reflexes were brisk and the plantar response was absent. (All these findings were duplicated in the nephew.) Complete anesthesia was present over the area of distribution of the internal popliteal nerve, and a boot of anesthesia was found over the lower portions of the legs. Vibration and position sense were poor in the legs. Speech was poorly articulated. There was no dysmetria or nystagmus.

The second patient is now 26 years old, was born prematurely at 8 months, had convulsions at the age of 10 months, walked when 30 months old and never went to school. Clubfoot was noted bilaterally at the age of 11, kyphoscoliosis soon after and gradual atrophy of the lower portions of the legs at 14, with no further change after the age of 20. On examination he showed a spastic-ataxic gait, with veering to the right. Some pseudohypertrophy of the muscles of the arms and marked amyotrophy of the legs were present. The tendon reflexes were absent in the limbs, the abdominal reflexes were brisk and the plantar response was not obtained. Vibration sense was very poor in all the limbs, and position sense was poor in the feet. Touch and temperature perceptions were poorly appreciated from the feet to the calves. Bilateral degeneration of the external popliteal nerves was demonstrated by electrical tests (reaction of degeneration). Biopsy of a nerve-muscle preparation showed marked demyelination and muscle atrophy. Unlike the findings in the first case, nystagmus and hypermetria were present.

HOLT, Worcester, Mass.

ZOSTER AND SPINAL DISEASES. M. KOBRO, Acta med. Scandinav. **104**:1 (April 23) 1940.

Kobro observed 6 patients with vertebral lesions in whom zoster developed in segmental relation to these defects. One patient presented zoster scars in the third and fourth cervical segments, and roentgenographic examination disclosed ankylosis of the second and third cervical vertebrae. Another patient had destruction of the fifth thoracic vertebra due to myelomatosis, and zoster developed in the fifth thoracic segment. A third patient had Hodgkin's disease with involvement of the sixth thoracic vertebra, and zoster appeared in the sixth thoracic segment. Another patient had spondylolisthesis between the fourth and the fifth lumbar vertebra, and zoster developed in the fourth lumbar segment. The objection may be made that the concurrence of zoster with vertebral lesions is a coincidence. However, each added case makes it seem more probable that a causal relation exists. The 6 cases of regional zoster with vertebral disease have been found among a limited number. A methodic search was made for patients with vertebral lesions and zoster that was not in segmental relationship, but none were found. Zoster in patients with vertebral lesions was always in segmental relation to the vertebral defects. It thus appears that a vertebral lesion may give rise to regional zoster, and since vertebral lesions may exist for a time without symptoms, the appearance of zoster should direct attention to the possibility of a vertebral lesion. The fact that zoster is not a common, but only an exceptional, complication of vertebral lesions indi-

cates that a ganglionic lesion alone cannot provoke zoster but that there must be another factor, and it is believed that this is the specific virus of zoster. The nonspecific lesion seems only to prepare the milieu for the specific virus of zoster.

J. A. M. A.

Vegetative and Endocrine Systems

A Case of Acromegaly Studied During the Course of the Disease and at Autopsy. G. Flaum and E. P. Ralli, Endocrinology **26**:229 (Feb.) 1940.

Since the original monograph by Cushing and Davidoff on acromegaly, there have been relatively few complete reports of this disease in which the patients have been followed for some time and the clinical observations correlated with the postmortem findings. The disease, however, is a well defined clinical condition which can definitely be related to hypersecretion of a hormone of the anterior lobe of the pituitary, and it is surprising that the literature does not contain more detailed reports of such cases. The case reported is that of a white woman aged 34 who was first seen two years after the onset of symptoms and who was followed closely until her death, three years after she was first admitted to the hospital. She had glycosuria and hypertension, in addition to the more or less typical symptoms of acromegaly. Roentgen examination revealed an enlarged sella turcica. The diagnosis was made of eosinophilic tumor of the pituitary with diabetes mellitus; operative removal of the tumor was advised, but the patient refused permission. Irradiation of the region of the pituitary was given for a period of three months. The course, however, was progressively downhill for the next three years, and the patient died approximately five years after the onset of symptoms. At autopsy the lesions were observed to be limited to the pituitary and the ovaries. In the former an adenoma consisting solely of eosinophilic cells was present, while the ovaries were atrophic.

The authors point out that the hypertension, which apparently was the precipitating factor in the patient's death, was not a part of the acromegaly but a distinct complication, as the eosinophils per se apparently do not secrete a pressor substance. On the other hand, in cases of basophilic tumors of the anterior lobe of the pituitary hypertension is the usual finding and is considered a part of the syndrome.

Palmer, Philadelphia.

Macrogenitosomia Præcox Associated with Hyperplasia of the Androgenic Tissue of the Adrenal and Death from Corticoadrenal Insufficiency. L. Wilkins, W. Fleischmann and J. E. Howard, Endocrinology **26**:385 (March) 1940.

Wilkins, Fleischmann and Howard describe in detail the case of a boy aged 3½ who had precocious development of the male accessory sex organs, the abnormal enlargement of the penis and scrotum dating from birth. The child was mentally defective, resistive and uncooperative, and expressed himself only in unintelligible sounds. The family history was not remarkable except that a sibling had presented the characteristics of a female pseudohermaphrodite. In addition to the abnormalities previously mentioned, the patient had moderate pigmentation of the skin and gums, low sodium and markedly elevated nonprotein nitrogen contents of the blood and a craving for salt. Death occurred suddenly, approximately one week after admission. The adrenal cortex was observed to be composed largely of androgenic or prenatal zone cells, which apparently had replaced other elements of the cortex to such a degree that death resulted from acute adrenal insufficiency. In the authors' opinion, this supports the theory that the androgenic zone has a function different from the portions of the cortex which control the electrolyte balance.

Palmer, Philadelphia.

THE EFFECT OF ANTERIOR PITUITARY-LIKE SEX HORMONE ON THE BLOOD PICTURE IN MAN. W. M. MOFFAT, Endocrinology **26**:595 (April) 1940.

Moffat administered a single dose of chorionic gonadotropin (follutein) intramuscularly to each of 38 persons. White blood cell counts were made in the afternoon and again the next morning, immediately preceding injection, and then two, four, six, eight, fifteen and twenty-four hours after injection. Leukocytosis appeared in four hours, reached its greatest height in six or eight hours and then diminished, but did not disappear in twenty-four hours. The degree of leukocytosis was roughly proportional to the amount of chorionic gonadotropin given. In the subjects receiving 100 rat units the rise was from 30 to 51 per cent. In those receiving 200 rat units the rise was from 61 to 85 per cent. There was an increase in the absolute number of white cells of all types, with relative neutrophilia. After daily repeated doses the leukocytosis gradually diminished and eventually disappeared, but after an interval of two to three weeks it could again be elicited. The leukocytosis did not seem to be a protein or toxic reaction. The same effects were observed in both sexes. There was no change in the red cell count or in the hemoglobin concentration. PALMER, Philadelphia.

ENDOCRINE DWARFISM. R. L. SCHAEFER and F. L. STRICKROOT, Endocrinology **26**:599 (April) 1940.

The authors report a fourth observation on 18 patients with pituitary dwarfism studied and treated for periods of from ten months to six years and four months. Fourteen patients treated with preparations of the growth factor of the anterior lobe of the pituitary showed a greater increase in height than the normal increment for the time of treatment, while during periods of no treatment the gain was less than the normal increment. The average for the whole group of 18 patients was an actual total growth of 94.5 inches (240 cm.), as compared with a normal total increment of 70.36 inches (178.7 cm.). The authors believe that in cases in which pituitary dwarfism and infantilism are associated a preparation containing factors of the anterior lobe other than the growth hormone might be more efficacious. They also believe that in early adolescence sexual underdevelopment is more important than moderate statural deficiency and should be given preference in treatment. The state of epiphysial closure as an indication of how much longer growth will remain possible is a factor in the decision as to the indication for treatment with the growth hormone. PALMER, Philadelphia.

THE RELATION OF THE ANTERIOR PITUITARY GLAND TO CARBOHYDRATE METABOLISM. F. G. YOUNG, Brit. M. J. **2**:393 (Aug. 19) 1939.

There is experimental evidence to substantiate the theory that the pituitary gland plays an important part in the control of carbohydrate metabolism. It is now believed that the anterior rather than the posterior lobe is responsible for the regulation of insulin sensitivity. Experiments have demonstrated that the influence of the pituitary gland on carbohydrate metabolism is to intensify those processes which taken in excess lead to diabetes.

The effect on carbohydrate metabolism of hypophysectomy and that of the administration of anterior pituitary extracts are intimately related. The diabetic condition has been induced experimentally by the administration of anterior pituitary extract, and hypophysectomy has alleviated this condition. It would appear that secretions of the anterior lobe of the pituitary depress carbohydrate oxidation in the muscles and promote storage of glycogen both from exogenous carbohydrate and from endogenous protein. Anterior pituitary extract increases the amount of islet tissue of the pancreas. Ketogenesis follows the injection of anterior pituitary extract.

Treatment with anterior pituitary extract diminishes carbohydrate oxidation in the muscles and promotes formation of sugar from protein in the liver. There

is still controversy as to how many different anterior pituitary substances influence the control of carbohydrate metabolism. The author believes that some patients exhibit an insulin-resistant diabetic condition of anterior lobe origin.

ECHOLS, New Orleans.

DIABETES MELLITUS AND THE HYPOPHYSIAL-THALAMENCEPHALIC SYSTEM. G. KÖHNE, Endokrinologie **22**:241, 1939.

Köhne made postmortem examinations in 12 cases of diabetes. Special attention was paid to the hypophysial-thalamencephalic system. Changes, such as island atrophy, sclerosis, lipomatosis and inflammatory processes, were observed in the pancreas in all cases. In 1 case in which there was acromegaly an eosinophil cell tumor of the anterior lobe of the hypophysis occurred. In 1 case of apparently extrainsular origin necrosis in the anterior lobe of the hypophysis was observed. The author points out that the conception of a central genesis of diabetes is too narrow and does not do justice to the complicated course of carbohydrate metabolism carried out by the synergistic action of several endocrine organs. However, this does not mean denying the existence of glycosuria of central origin. The author concludes that the cause of classic diabetes does not lie primarily in the hypophysial-thalamencephalic system. J. A. M. A.

PATHOGENESIS OF CUSHING'S SYNDROME. J. JACOBI and F. TIGGES, München. med. Wchnschr. **86**:1665 (Nov. 24) 1939.

Jacobi and Tigges say that Cushing designated this syndrome "pituitary basophilism" because in 11 of 14 cases he observed a basophilic adenoma of the anterior lobe of the pituitary which he regarded as the cause of the disease. This opinion has been challenged, but before they explain their own stand on this problem the authors report 2 cases of the syndrome. The first case was characterized by an increase in the corticotropic hormone, by hypertrichosis and by hyperphosphatemia due to increase in organic phosphorates. In the second case the corticotropic hormone was likewise increased, but there was no hypertrichosis and the hyperphosphatemia was due to an increase in lipoid phosphorus. It is noteworthy that in the first case necropsy failed to disclose an adenoma of the hypophysis but did reveal hypertrophy of the adrenal glands with circumscribed adenomas in the cortex. The authors review the leading opinions regarding the pathogenesis of Cushing's syndrome and show that these raise the following questions: Are Cushing's syndrome and interrenalism identical? Is the basophilism primary or secondary? Is the hyperplasia of the adrenal cortex primary, or is it the result of an increase in the interrenotropic (corticotropic hormone of the hypophysis) hormone? Can Cushing's syndrome develop without increase in the interrenotropic hormone? The authors assume that in the majority of cases Cushing's syndrome is caused by a functional disturbance in the anterior lobe of the pituitary with an increase in the interrenotropic hormone. This excess in interrenotropic hormone leads to an increase in the hormone of the adrenal cortex, usually with simultaneous hyperplasia of the cortex, and thus to Cushing's syndrome. Less often, when there is no increase in the interrenotropic hormone, the development of Cushing's syndrome is presumably the result of primary hyperfunction of the adrenal cortex (tumors of the adrenal cortex). The significance of basophilism is still obscure because it has been absent in cases of Cushing's syndrome in which there existed an increase in the corticotropic hormone. Only a careful search for the corticotropic hormone and a comparison with histologic changes will further clarify the pathogenesis of Cushing's syndrome. Clinical methods will reveal the hormone, but not the anatomic changes in the pituitary or the adrenal glands. The aforementioned explanation of the pathogenesis has therapeutic significance. In a number of cases of Cushing's syndrome, roentgen irradiation of the pituitary has produced good results. The authors believe that the success or failure of this therapy is chiefly dependent on whether or not the

rays are applied to the organ in which the primary process exists; that is, if the primary disorder is in the adrenal glands, irradiation of the pituitary will give no prospect of cure, though irradiation or surgical treatment of the adrenal glands will do so.

J. A. M. A.

Treatment, Neurosurgery

MANAGEMENT OF FACIAL PARALYSIS BY PHYSICAL MEASURES. M. K. NEWMAN, J. M. BERRIS and S. S. BOHN, Arch. Phys. Therapy **21**:270 (May) 1940.

Newman and his co-workers state that the treatment of paralysis of the facial nerve is dependent on its various etiologic factors, on the question of whether the paralysis is of central or of peripheral origin and on the site of the lesion. They managed 30 patients by the use of physical therapeutic measures. The ages of the patients ranged between 6 and 79 years, the average age being 37. With the onset of an acute refrigerans type of facial paralysis iodides in saturated solution of potassium iodide or syrup of hydriodic acid are indicated for their general alterative action. Analgesics are valuable. Saline laxatives are used during the acute stage of inflammation for their possible detergent effect. The physical measures applicable during the acute phase of the refrigerant palsy are directed toward the reduction of the inflammatory exudate and toward keeping the denervated muscles in a position of physiologic rest. Decongestion at the stylomastoid foramen can be accomplished by cantharides plasters, hot moist applications, radiant heat, negative galvanism and conventional or short wave diathermy. The frequency of application is indicated by the pain and the tolerance of the tissues. To prevent muscles from stretching, they are supported by attaching two Y bands of adhesive tape at the zygomatic bone and temporal region. Positive galvanism is especially efficacious for the relief of pain. With the subsidence of the acute symptoms within eight to ten days, testing for reaction of degeneration is instituted. When no reaction of degeneration is present, recovery can be expected in from two to eight weeks. If a sufficient amount of recovery is not obtained after six months of rigorous physical therapeutic measures, surgical intervention is to be considered. Active treatment now consists of heat, massage, voluntary exercise and electrical stimulation (with interrupted galvanic, sinusoidal and faradic currents). Diathermic or radiant heat is applied to the paralyzed side of the face for from fifteen to thirty minutes. Another method of promoting a circulatory response consists of the common ion transfer of 0.5 per cent acetylbetamethylcholine hydrochloride. From 15 to 20 milliamperes of the galvanic current for twenty minutes is adequate. Negative galvanism, for its heating effect, can be applied for thirty minutes over the stylomastoid foramen. The strength of current should be just less than the amount required to cause a contraction of the muscles on the unaffected side. On the first day three contractions over the motor points are sufficient, and on subsequent days the number of contractions is increased but always kept within the fatigue range of the muscle. After one or two weeks the slow sine wave current is substituted, from twenty to thirty contractions per minute being used. When the faradic current can be tolerated, it should replace the sine wave current. Gentle stroking massage, which follows stimulation, preserves muscular tone. Exercise of the facial muscles is carried out in front of a mirror every day. The etiologic agent must always be removed before physical measures are instituted. In 17 of the 30 cases the paralysis followed exposure; in 6, disease of the middle ear; in 1, dental manipulation; in 1 trauma associated with an automobile accident; in 2 head colds; in 1, mumps; in 1 an operation on the eighth nerve for vertigo; in 1, postpartum infection, and in 2, mastoidectomy. In the 17 cases of paralysis due to exposure, partial or no reaction of degeneration was present after ten days. Eight of these patients received only heat, massage and exercise, while the remainder received electrical stimulation as well.

J. A. M. A.

TESTOSTERONE PROPIONATE AND THE MALE CLIMACTERIC. H. B. THOMAS and R. T. HILL, Endocrinology **26**:953 (June) 1940.

Thomas and Hill report 2 cases of patients with conditions diagnosed as the male climacteric (involutional melancholia) who were treated with moderate doses of a synthetic androgen (testosterone propionate). Both patients made remarkable improvement during treatment and have maintained this improvement for seven and ten months, respectively, after cessation of the injections.

The first patient, a white man aged 56, married, presented the usual picture of involutional melancholia—depression, mental confusion, nervousness, insomnia and delusions of persecution. Other physical findings were without significance, and the family history was not remarkable. He was given 10 mg. of testosterone propionate three times a week for four weeks and then 10 mg. twice a week for six weeks, after which he was discharged as cured. For the past seven months he has been normal.

The second patient, a white man aged 48, was given 10 mg. of testosterone propionate once a week for eight weeks, after which time he received no further treatment. He has shown marked improvement, which began during the course of the treatment and has continued for the past ten months.

The authors feel that in view of these satisfactory results study of additional patients with similar treatment is warranted when the causative factor is the male climacteric.

PALMER, Philadelphia.

TREATMENT OF MENTAL DISORDERS WITH MALE SEX HORMONE [ANDROGEN]. A. GUIRDHAM, Brit. M. J. **1**:10 (Jan. 6) 1940.

Guirdham used testosterone propionate and androsterone benzoate in the treatment of 4 mentally disordered male patients. With 1 partial exception, there was no hypogonadism present. In the first patient the first beneficial mental effects from the treatment embodied rapid transition from a psychotic to a psychoneurotic state. Acute anxiety and obsessive tendencies were dispelled. The second patient improved far beyond expectations. In addition to profound obsessional tendencies and early signs of schizophrenia, there were such legal complications as theft. In the third patient, a man aged 74, anything more than the most inconsiderable alleviation of symptoms could not be expected, as he had gross arteriosclerosis with melancholia and delusions of visceral function and financial ruin. The fourth patient was profoundly hypochondriacal before treatment was initiated. The prognosis in 2 of these cases was considered hopeless. Conditions of undoubted gravity have been remedied. Treatment with "sex hormones" is a rational procedure for postclimacteric conditions. The author believes that the form of psychoneurotic symptoms is largely determined by the degree of stability shown by the vegetative nervous system, and that this in turn is dependent on glandular activity.

J. A. M. A.

EPILEPSY TREATED WITH EPANUTIN [DILANTIN SODIUM]. A. J. M. BUTTER, Brit. M. J. **1**:483 (March 23) 1940.

During the past year, 43 sane male epileptic patients were treated with varying doses of dilantin sodium (sodium 5,5-diphenylhydantoinate); 27 (63 per cent) of them had few subsequent fits and a better psychologic outlook. Probably the most successful therapeutic dose is 3 capsules a day. The author noted that age had nothing to do with the success of the treatment, but it appeared that patients of low grade mentality were less likely to be benefited by this treatment and more likely to manifest toxicity than those of average intelligence. Toxic symptoms, such as pyrexia, cutaneous rashes, hypertrophic gingivitis, tremulousness, intention tremor, ataxic gait, nystagmus, ptosis, slurring speech, insomnia and mental confusion, were observed, but these disappeared within a few days after cessation of treatment.

ECHOLS, New Orleans.

CLINICAL EXPERIENCE IN ELECTRICALLY INDUCED CONVULSIONS. FRANCIS E. FOX, Brit. M. J. **1**:807 (May 18) 1940.

Fox advocates the production of shock by electrically induced convulsions three times a week in treating selected psychotic patients. However, this form of therapy is contraindicated in the presence of arterial and cardiac diseases, high blood pressure and intracranial diseases. He records the histories of 7 patients with various psychotic disorders receiving this type of shock therapy. Five of the 7 patients returned to their normal routine and enjoyed ordinary social intercourse outside a hospital for mental disease. Two patients showed sufficient improvement in behavior to permit them to frequent the higher spheres of hospital life.

Although the author admits the uncertainty of the ultimate prognosis of this form of treatment, he believes that the remissions can be prolonged indefinitely by "maintenance" shocks (three in a single week) if the patient is found to be suffering a relapse. He enumerates the advantages of this form of treatment over other forms of convulsive therapy: The patient suffers no unpleasant memories; the loss of consciousness is instantaneous as soon as the lever is pressed; the possibility of fracture is remote provided proper precautions are taken; the patient is willing to cooperate after the first two or three shocks; the treatment is quickly given; the appetite is stimulated and body weight increases; chronic constipation disappears early in the treatment; the apparatus is portable, and the manipulator need not be a highly qualified electrical technician.

ECHOLS, New Orleans.

ACOUSTIC TUMOURS. H. OLIVECRONA, J. Neurol. & Psychiat. **3**:141 (April) 1940.

The immediate, and especially the late, results of operation for acoustic tumors are hardly known. In summarizing his operative results in 130 cases of acoustic tumors from 1930 to 1939, Olivecrona finds that the immediate mortality rate in his series was 21.5 per cent and the remote mortality rate 8.8 per cent. Both the immediate and the remote mortality rate were lowest when the tumor was completely extirpated; subtotal extirpations had a less favorable prognosis, and intracapsular enucleations were followed by the highest mortality. Intracapsular enucleation gave excellent results only in cases of cystic or stationary tumors; otherwise, the neoplasm tended to recur. The postoperative morbidity rate, as measured in terms of capacity for work, showed in general that immediate return to full earning capacity was rare. The majority of patients with radical and subtotal extirpations were left with some defect which limited their capacity for work, but these defects gradually disappeared if sufficient time was allowed for convalescence and reeducation. The morbidity rate was lowest in the group of patients with intracapsular enucleations, but this was apparent only, since in this group patients with stationary tumors alone survived, the others having died of recurrence. With the development of better technic Olivecrona gradually lowered the mortality rate for complete extirpation from 26.3 per cent, in 1931 to 1933, to 11.1 per cent, in 1937 to 1939; the frequent postoperative complication of facial palsy also was prevented in 65 per cent of the cases. The author concludes that, with the exception of cystic tumors, complete removal of an acoustic tumor should be attempted in all cases.

MALAMUD, Ann Arbor, Mich.

TREATMENT OF MENINGOCOCCIC MENINGITIS WITH SULFANILAMIDE COMPOUNDS. A. RUSESCO, V. VOICULESCO and A. DIACONU, Presse méd. **48**:471 (May 8-11) 1940.

The authors treated 10 patients with epidemic cerebrospinal meningitis, 8 with soluseptasine (a benzylsulfanilamide derivative; disodium p-[γ-phenylpropylamino]-benzenesulfonamide-α-γ-disulfonate) in a 6 per cent solution and 2 with serum and azosulfamide (disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxy-naphthalene-3',6'-disulfonate) in a 2.5 per cent solution. Nine recovered and 1 died.

Five were nurslings, aged from 2½ to 11 months, and the others ranged in age from 2½ to 13 years. The drug was given intraspinally, intramuscularly and in 1 instance orally. The disease lasted from two to seven days. Soluseptasine was administered in decreasing doses as the patient's condition improved. Single injections amounted to from 10 to 15 cc. intraspinally and from 10 to 20 cc. intramuscularly in nurslings and approximately twice this amount in older children. The total dose of the substance was from 15 to 23 Gm. for nurslings and from 25 to 34 Gm. for the other children. To avoid relapse, prolongation of treatment to fifteen days is advisable. The authors recommend treatment of meningococcic meningitis with sulfanilamides exclusively and suggest combining it with serotherapy only in case the sulfanilamide is not well tolerated. Study of the literature reveals that the statistics for intraspinal and for oral treatment are equally favorable. Intraspinal treatment is advised on account of its rendering possible the immediate concentration of the drug in the cerebrospinal fluid, even though of short duration, and because, in the opinion of some investigators, the inflamed meninges have a diminished permeability to sulfanilamides. Oral treatment is advised on account of the rapid elimination of intraspinally injected sulfanilamide and on account of the possible occurrence of meningococcic septicemia and encephalitis. In the presence of renal impermeability, administration into the blood is preferable. Sulfanilamide treatment gives a higher percentage of cures than serotherapy, particularly in nurslings. One should bear in mind that there are different strains of meningococci, some sensitive to sulfanilamides and others to serum. Meningococcus B infection should be treated with sulfanilamide. In the course of sulfanilamide treatment, cyanosis, cutaneous eruptions, digestive upsets and changes in the blood picture may occur. It is wise to examine the blood picture from time to time and check the complications.

J. A. M. A.

Casuistic Contribution to Treatment of Tabetic Crises: Insulin in Control of Lancinating Pains. H. Binswanger, Schweiz. med. Wchnschr. **69**:1327 (Dec. 30) 1939.

Binswanger reports observations on a patient with severe tabetic crises, for whom only fever therapy was effective. However, the effects of the fever therapy were of short duration. Insulin shock therapy was resorted to, and after this the tabetic crises subsided for a time. When the pains recurred it was decided to try to counteract the crises by "weakened" administration of insulin. It was found to be sufficient for the hypoglycemia to produce slight somnolence and profuse sweating. The insulin should be extended over a period of from two to three weeks and should be begun when the tabetic pains have been absent for several days, for attacks of lancinating pains, persisting for several days, apparently cannot be broken off by insulin therapy. The insulin treatment improves the general condition and puts the patient into a euphoric mood. If insulin should prove effective in other cases of tabes with lancinating pains, it would be a distinct advancement in the treatment of painful tabetic crises.

J. A. M. A.

Sulfapyridine in Treatment of Epidemic Meningitis. W. Jäckli, Schweiz. med. Wchnschr. **70**:280 (March 30) 1940.

Treatment of epidemic meningitis at the children's hospital in Zurich consists, according to Jäckli, of oral administration of sulfapyridine in a daily dose of 1 Gm. for each 10 Kg. of body weight. This quantity is distributed evenly over the twenty-four hours at four hour intervals. The medication is continued until the cerebrospinal fluid is clear (from 50 to 150 cells per cubic millimeter) and meningococci are no longer demonstrable, which is usually the case in from two to five days. The dose is gradually decreased and the medication is terminated between the eighth and the twelfth day. The individual doses at the onset are somewhat larger in order to reach the desired concentration in the blood and cerebrospinal fluid as soon as possible. Lumbar punctures are made twice a day

in the beginning, control punctures occasionally. The treatment is often begun with a blood transfusion. Serum is not given. Cardiac and circulatory stimulants are employed according to need. Intramuscular injections of sulfapyridine are employed when oral medication is not tolerated. Administration of sulfapyridine by intravenous drip is another valuable mode. It makes possible the administration at the same time of nutrient substances and fluids. It is reserved for comatose patients and for patients with primary uncontrollable vomiting. The daily dose of sulfapyridine sodium is added to the infusion fluid of a 5.5 per cent solution of dextrose in Ringer's solution. Cardiac and circulatory stimulants may be added to the infusion fluid. The drip infusion is continued only as long as absolutely necessary, usually from two to five days. The author employed this therapy for 16 children with epidemic meningitis admitted during the epidemic of December 1939 to February 1940. The ages of the children varied from 6 months to 15 years. They either were completely cured or had advanced far in their convalescence at the time of the report.

J. A. M. A.

TREATMENT AND CAUSE OF NOCTURNAL ENURESIS IN CHILDREN. S. I. VAYNBAUM, Sovet. med., 1940, no. 2, p. 32.

Vaynbaum treated 122 children with nocturnal enuresis. The patients were examined by an ophthalmologist, a pediatrician, a laryngologist and a neurologist in order to exclude cases of myopia, tonsillar infection and helminthiasis. There were 21 patients up to 6 years of age, 79 up to 10 and 22 above 10 and below 15. There were 59 boys and 63 girls. The treatment consisted of daily injection into the gluteal muscles of a 25 per cent solution of magnesium sulfate in doses beginning with 0.5 cc. and increasing gradually up to 3 cc. Enuresis became less frequent after the first few injections and did not occur after from ten to fifteen injections. There were no untoward reactions. The patients were followed for from six months to one year. All but 4 were cured. Three etiologic groups were recognized. One group consisted of 10 patients with congenital syphilis. They were given antisyphilitic treatment, at the termination of which enuresis had disappeared. The second group presented a number of organic, dystrophic alterations and generally retarded development, suggesting that the cause of enuresis here was increased irritability of the detrusor muscle and weakness of the urinary bladder. The author does not exclude the possibility of congenital syphilis in this group as well. The rationale of magnesium sulfate therapy is based on the depressing effect of the drug on the central nervous system, the peripheral nervous system and the sensory nerve fibers. The treatment of enuresis calls for strict individualization because of the varied etiologic factors. Magnesium sulfate therapy appears to be successful in cases in which there is increased irritability of the detrusor muscle and spastic bladder.

J. A. M. A.

Muscular System

STUDIES IN DYSTROPHIA MYOTONICA. JAMES J. WARING, ABE RAVIN and CHARLES E. WALKER JR., Arch. Int. Med. **65**:764 (April) 1940.

Waring, Ravin and Walker report 13 cases of dystrophia myotonica, with charts showing the incidence of the disease in families. The inheritance is explained as a dominant mutation which is at first manifested by very few signs, either because the condition is mild or because the patients succumb in a short time. The disease sets in at increasingly earlier ages in successive generations and becomes gradually more severe until finally the complete syndrome manifests itself. It has been noted that cataracts are found in the generations preceding the dystrophic generations.

The onset is insidious and the progress is usually very slow. Since the myotonia is not disabling, the presenting complaint is usually weakness. The myotonia

occurs mainly in the muscles of the forearm and hand, where it is manifested by inability to relax promptly. The difficulty in relaxing becomes less with each repetition of the contraction. The myotonia is not painful but increases in degree with increase in the force of contraction. The contractions characterized by myotonia are voluntary contractions, mechanical myotonia, produced by striking the muscle with a percussion hammer, and electrical myotonia, characterized by persistence of the contraction after cessation of the stimulating current.

The atrophy may or may not affect muscles which have shown myotonia, such as the muscles of the face, the sternocleidomastoids, the muscles of the forearm, the quadriceps and the dorsiflexors of the foot. The so-called myopathic facies results from atrophy of the temporal muscles, the orbicularis ori and the orbicularis oculi on both sides. As the disease progresses, other muscles become atrophic and the patient appears markedly emaciated. Fibrillary twitchings are not observed. The tendon reflexes disappear as the atrophy progresses. The vibratory sense has been reported as being impaired, but sensation is otherwise normal.

Of the 13 patients reported on, 12 had cataract. These develop slowly and are indistinguishable from other types of mature cataracts. Chronic ulcerating blepharitis and chronic conjunctivitis are common complications.

Testicular atrophy is frequently present and results in impotence and infertility. Menstrual irregularity and infertility follow from involvement of the ovaries. The thyroid is often enlarged and firm. The basal metabolic rate is usually low, but the cholesterol content of the blood is normal. The low basal metabolic rate, the testicular and ovarian dysfunction, the emaciation and the alopecia suggest the possibility of a primary pituitary dysfunction.

No constant mental changes were found in the authors' series, but other workers report low intelligence levels in patients with dystrophia myotonica. Bradycardia, hypotension and electrocardiographic abnormalities are rather constant. The disease must be differentiated from myotonia congenita, from the various progressive muscular atrophies, from diseases producing presenile cataract and from various endocrine disorders.

Since the disease becomes more severe in successive generations voluntary celibacy is advocated. Improvement in the myotonia is produced by quinine and epinephrine. The muscular atrophy has not proved amenable to any form of treatment, but patients report subjective improvement with aminoacetic acid, epinephrine and epinephrine and pilocarpine. The cataracts are treated surgically.

BECK, Buffalo.

Basal Ganglia

TWO CASES OF PARKINSONIAN SYNDROME RESULTING FROM ELECTRICAL INJURY. MAX H. WEINBERG, J. Nerv. & Ment. Dis. **90**:738 (Dec.) 1939.

After receiving an electric shock while using a telephone, Weinberg's first patient, a man aged 47, became nervous, had pains in the head and experienced involuntary "twisting" movements of the right hand. Two years later examination revealed deafness of the left ear, rigidity of the right arm and leg, athetosis and loss of associated movements in the right upper extremity and a rapid tremor of both arms. Five years later the findings were unchanged, and a suggestively pathologic plantar response had appeared on the right. In the second case, a woman aged 44 was unable to use the right hand immediately after receiving an electric shock while inserting a plug into a wall connection, and half an hour later could not speak. Five days later speech was slurred; rigidity and hyperreflexia were present in the right arm and leg, and positive Hoffmann and Babinski reactions were present on the right side. Five months later both lower extremities were spastic, the plantar response was pathologic on both sides, and associated movements were diminished in the right arm. Weinberg considers that the neurologic changes were due to electric shock in both cases.

MACKAY, Chicago.

MYOCLONUS EPILEPSY WITH PRIMARY OPTIC ATROPHY. M. P. ROSENBLUM and H. HERMAN, J. Nerv. & Ment. Dis. **91**:456 (April) 1940.

Rosenblum and Herman report what they believe to be the first recorded case of myoclonus epilepsy associated with primary optic atrophy. The patient, a Jew aged 35, had begun during the first year of his life to have convulsions, which were followed soon by myoclonic twitchings. At first the seizures occurred several times a day, but they became progressively less frequent, while the myoclonus became more pronounced. When he was 11 years old progressive amblyopia began. The family history was without significance. The myoclonic contractions were generalized, but involved particularly the face, neck, pharyngeal muscles and diaphragm, producing a respiratory grunt and explosive speech. They were intensified by emotion and effort. There was an intention tremor, with primary optic atrophy, concentric contraction of the visual fields and large central scotomas. Vision was reduced to counting fingers. Nystagmus was present on lateral gaze. The intelligence quotient was 65, and there were anxiety manifestations and hypnagogic hallucinations. Roentgenographic and laboratory examinations gave normal results. The authors consider the condition an abiotrophy.

MACKAY, Chicago.

HEREDOPATHIC COMBINATION OF A CONGENITAL DEFORMITY OF THE NOSE AND OF MYOCLONIC TORSION DYSTONIA. L. BENEDEK and E. RAKONITZ, J. Nerv. & Ment. Dis. **91**:608 (May) 1940.

Benedek and Rakonitz report the heredofamilial occurrence of combined developmental retardation of the nasal bones and a form of myoclonus and torsion dystonia in three generations of the same family. A mother and her 2 sons, all affected, were examined; her maternal aunt was known to have had the same abnormalities. The nasal anomaly consisted of a median nasal groove, similar to that seen in certain anthropoid apes (Simia satyrus L.), with hypoplasia of the minor and major alar, the septal and the lateral cartilages. The motor disturbances consisted of rapid, spontaneous, arrhythmic, involuntary contractions of the broad, flat muscles of the shoulders, neck and back, without resulting motion of the extremities (myoclonus) and, in addition, torsion spasm of the muscles of the neck and trunk. The patients examined also exhibited enlargement of the accessory nasal and mastoid cavities and infantilism and sclerotization of the larynx. The nasal and laryngeal abnormalities were equally manifest in all the affected persons, but the intensity of the motor disturbances varied from one patient to another. Emotional factors influenced both the myoclonus and the torsion dystonia. Benedek and Rakonitz consider the whole complex heredopathy to be due to a developmental disturbance of the mesencephalon and diencephalon during the first three or four months of embryonic growth.

MACKAY, Chicago.

MYOGRAPHIC STUDIES OF EXTRAPYRAMIDAL HYPERKINESIAS. F. STUHLMÜLLER and G. SCHALTENBRAND, Deutsche Ztschr. f. Nervenh. **150**:1, 1939.

Stuhlmüller and Schaltenbrand have applied the latter's well known method of mechanical myography to study of the extrapyramidal hyperkinesias and have made observations in 21 cases of Sydenham's and Huntington's chorea, torticollis, athetosis and ballism. They found in the two choreas no typical frequency of twitches. It was impossible by the method used to distinguish between Sydenham's and Huntington's chorea. On the whole, in the choreas, the twitches are faster and more explosive and are separated from each other. They are thus distinguished from those in athetosis and torticollis, which are slow and blend into each other. In hemiballism both single jerks and fast sequences of jerks were recorded. In a great number of instances hypotonia was found, in 1 instance on the more severely involved side. No periodic movements were seen in any of the cases, and there was always involvement of antagonist muscles, such as flexors and extensors. Mobile spasm was seen in a number of cases of various conditions.

HOEFER, New York.

Society Transactions

NEW YORK AND PHILADELPHIA NEUROLOGICAL SOCIETIES

Joint Meeting, April 26, 1940

Relation of Calcium and Potassium to Certain Aspects of Neuromuscular Function. Dr. A. M. Harvey, Dr. R. L. Masland, Dr. R. S. Wigton and Dr. George D. Gammon, Philadelphia.

For the maintenance of the normal excitability of nerve and muscle fibers and the transmission of the excitatory impulse across the synapse, both at the neuromuscular junction and in the sympathetic ganglion, the proper ionic balance must be present, particularly that of calcium and potassium. We shall discuss briefly certain abnormalities in neuromuscular function which result from disturbances in calcium and potassium balance and shall consider how these are related to the development of symptoms in certain clinical conditions.

Studies have been made concerning the functional properties of peripheral nerves by electrical methods during periods of normal and of reduced values for blood Ca++ in cases of parathyroid tetany. The threshold to stimulation by electric currents is markedly decreased, as is well known when the blood Ca++ is low and signs of tetany are evident. Even smaller changes in the functional characteristics of peripheral nerves can be determined quantitatively by observing the relative rise in threshold when slowly increasing currents are used for stimulation. By use of this type of stimulation a measure of the property of accommodation of nerve is determined. It was found that definite and characteristic changes in the activity of the nerve accompanied these alterations in blood calcium level and that these changes could be detected before any alterations in clinical signs or blood calcium values were apparent.

When one perfuses a sympathetic ganglion in the absence of calcium ions long-continued, spontaneous activity of both the ganglion cells and the preganglionic fibers is set up. At the same time, however, there develops failure of transmission of excitation from the synaptic endings of neurons. We have been able to demonstrate that during this period of failure of synaptic transmission the normal liberation of acetylcholine from the preganglionic nerve endings does not take place. Similarly, in the presence of low calcium values the action of the vagus nerve in slowing the heart is abolished and again the normal liberation of acetylcholine from the nerve endings is interfered with.

We see, therefore, that upsetting the normal calcium relationships causes the nerve tissues to be abnormally excitable and, if the deficiency is severe enough, spontaneous activity will appear. At the same time the mechanism for transmission at synaptic junctions is interfered with.

If the calcium deficiency is produced by diet and develops over a longer period a different picture is produced. The spontaneous activity is not evident until just before death, and the most obvious defect is in synaptic transmission. A maximal motor nerve volley will excite only a fraction of the muscle fibers which it innervates, but leaves behind it a period of raised excitability so that a second impulse coming a short time afterward produces an almost normal response.

The effects of altered calcium-potassium balance on the muscle fiber itself are equally striking. The response of the muscle to a small stimulating dose of potassium is enormously increased by lowering the calcium content of the medium surrounding

the muscle. Drugs which alter the available calcium, such as guanidine and veratrine, produce a similar effect, and their action can be counteracted by a small excess of calcium ions.

The similarity between veratrinized muscle and the myotonic muscle is close. We have been able to study the responses of the myotonic muscle both electrically and myographically in a series of goats suffering from a form of congenital myotonia which is indistinguishable from Thomsen's disease as it occurs in the human being. The myotonic muscle is exquisitely sensitive to potassium ions, and myotonia can be readily abolished by small amounts of calcium injected directly into a myotonic muscle. Also, desoxycorticosterone, which alters the potassium regulation, has been found, when given in large doses, to abolish myotonia in the goat.

The change in muscle function which is so evident in periodic family paraylsis has also been shown to be intimately bound up with changes in potassium. During an attack the serum potassium level is low, and return to normal function follows the administration of potassium.

Thus, the excitability of both nerve and muscle fiber is intimately bound up with the calcium and potassium content of the tissues, as is also the ability of nerve impulses to pass across synaptic junctions. This ionic balance may be influneced by many factors, and an understanding of the changes produced under various circumstances should both advance knowledge of fundamental neuromuscular mechanisms and clarify the pathogenesis of symptoms in many clinical conditions.

DISCUSSION

Dr. Foster Kennedy, New York: In pharmacologic experiments with myotonia congenita, carried out by Dr. Alexander Wolf and myself, it was discovered that quinine is a specific temporary antidote for myotonia and that it was possible to prove that the lesion lay either in the neuromuscular junction or in the muscle itself. We hoped that these facts regarding the control by quinine of chemical changes in the neuromuscular mediator would furnish a key to further information regarding the physiology of neuromuscular action.

I should like to point out that acetylcholine is more abundant in the basal ganglia than in the cortex and to suggest that the fluctuations in sympathetic-parasympathetic drives which lie at the bottom of many neuroses, and indeed psychoses, such as manic-depressive conditions, might depend for their production on altered chemical condjtions in the basal ganglia and the hypothalamus.

Dr. Mary E. O'Sullivan, New York: I have little to add to Dr. Kennedy's discussion of this important work. Such physiologic experiments as these will be of unlimited aid in the progress of clinical neurology. I have noted that in many tense, "high-strung" patients suffering from symptoms of a so-called neurotic character tetanic-like twitches of the muscles of the face, positive Chvostek and Trousseau signs, and the like rapidly developed after inhalations of carbon dioxide and oxygen. The symptoms of nervous tension in these patients are relieved by large doses of calcium when administered with vitamin D or parathyroid extract.

Such experimental work as this adds to knowledge of the metabolism of calcium and its relation to the physiology of the nervous system. Further knowledge of these mechanisms will be of great value in solving some of the therapeutic problems in clinical neurology.

Dr. A. M. Harvey, Philadelphia: We have found that quinine relieves myotonia in goats. There is no evidence that neuromuscular transmission is involved in this condition. It seems that the muscle fibers themselves are abnormally sensitive to potassium and that there is also a normal release of potassium when the muscle contracts. Owing to the exquisite sensitiveness of myotonic patients to potassium, the persistence of the muscular contraction may be attributed to this normal release of the element from the muscle tissue.

Further Observations on Meningorachidian Phlebitis. Dr. Temple Fay and Dr. Frank Konzelmann, Philadelphia.

In June 1937 one of us (Fay) reported before the American Neurological Association 3 verified cases of meningorachidian phlebitis in which was presented a clinical syndrome described by Spiller as "epidural ascending spinal paralysis" (Spiller, W. G.: Epidural Ascending Spinal Paralysis, *Rev. Neurol. & Psychiat.* **9**:494 [Sept.] 1911).

Reports of cases 1, 2 and 3 in this presentation were published in detail, and the clinical syndrome associated with the onset and progress of the disease was noted (Fay, T.: Epidural Ascending Spinal Paralysis ["Spiller's Syndrome"], *Confinia neurol.* **1**:162 [May] 1938).

The outstanding symptom in this group was pain, confined to the nuchal, midthoracic or lumbar area, for variable periods followed by rather sudden and progressive weakness with atrophy. The atrophy of the muscles of the hands, arm and lower extremities is the most striking objective finding. It simulates that in progressive poliomyelitis. In fact, in 1 case the diagnosis was Landry's paralysis, in another case chronic poliomyelitis, because of the pain and atrophy, and in 4 cases acute neuronitis. In 2 cases the diagnosis was peripheral neuritis and transverse myelitis, in 2 hysteria and syringomyelia.

The symptom complex (Spiller's syndrome) may be summarized as follows:

1. Pain in the back, chest or legs, due to involvement of the roots of exit. This may be localized or diffuse and may be easily mistaken for neuronitis or neuralgia, or even tabes.

2. Subsidence of the pain, with the appearance of weakness in the knees or sudden paralysis.

3. Subjective symptoms of numbness in the lower extremities or lower part of the trunk, associated frequently with objective findings (particularly hypothermesthesia), varying from slight impairment to complete loss of sensation.

4. Increasing weakness and paralysis, ascending toward the level of greatest involvement of the cord.

5. Incontinence and loss of bladder and sphincter control, in cases of paralysis.

6. Paradoxic signs of involvement of the upper and lower motor neurons, such as ankle clonus and the Babinski sign with marked diminution of the tendon reflexes, or profound atrophy of the muscle groups with increased reflexes or the Babinski sign and ankle clonus with loss of tendon reflexes and marked atrophy.

7. Profound atrophy at the level of greatest involvement of the cord and in the large groups of muscles situated below the level of the lesion.

8. Rapid or chronic progression of motor weakness to involve the upper extremities and even the muscles of the shoulder girdle and neck, at times simulating Landry's paralysis.

9. Tendency toward vasomotor and trophic disturbances, at and below the level of the lesion.

10. Slight variation of temperature from the normal.

11. Absence of positive signs in the Queckenstedt test early in the symptom complex.

12. Slight cellular reaction in the spinal fluid (1 to 12 white blood cells per cubic millimeter) with or without increase of protein.

13. Absence of signs of obstruction of the spinal canal on injection of air and in the myelogram.

14. Negative roentgenographic findings, aside from demineralization and scoliosis of the vertebrae below the level of the lesion.

15. Tenderness to percussion over the spinous processes at and below the level of the lesion.

16. Evanescent vasomotor manifestations in the dermatomeres supplied by the roots, at or above the level of the lesion.

17. A tendency for the symptoms and pathologic lesions to localize temporarily in the region between the third and the eighth thoracic vertebra, although cervical and lumbar involvement has been noted.

18. Occasional rapid ascension to higher segments of the level of involvement established at the first examination and occasional remission to the original level.

19. Progressive atrophy of the muscles, a striking characteristic.

20. Diffuse thrombophlebitis of the meningorachidian veins, revealed at operation or at autopsy, the degree of severity ranging from subacute involvement to purulent epidural abscess.

The paradoxic appearance of a Babinski sign in the absence of reflexes or the exaggeration of reflexes with the Babinski sign is characteristic. Atrophy of the small muscles of the hands and feet, marked weakness and pain cannot be overlooked in many abortive types in which one or more member may be involved.

Qualitative changes in sensation, particularly concerned with cold, and pain are important. Dermatomeres in the cervical area, as compared with the trigeminal field, frequently reveal not only vasomotor manifestations and pigmentation but hypalgesia or hyperalgesia, depending on the stage of inflammatory reaction.

In each of the cases presented, exploratory laminectomy was performed because of symptoms which tended to focalize the level of the lesion or, in 1 instance (case 2), in order to observe the progress of acute ascending paralysis (Landry's type) and to determine the lesions which might be present.

Streptococcus viridans was obtained in a culture of the spinal fluid in 3 of these cases and in a culture of the blood in 1 case. In the other cases the organisms found on culture were pneumococci, hemolytic streptococci, nonhemolytic streptococci and hemolytic staphylococci.

One patient in the series died, and all but 1 of the others have recovered sufficiently to be ambulatory and active. Patient 5, with transverse myelitis remains in the hospital although returning use of the upper extremities has been made possible by continued therapy with vaccine, sodium salicylates and high voltage roentgen irradiation.

DISCUSSION

DR. J. H. GLOBUS, New York: This instructive communication by Dr. Fay and Dr. Konzelmann is particularly significant because it draws attention once more to an important expanding lesion in the epidural space. For some reason, the syndrome did not assume a place in neurology in accordance with its clinical and pathologic significance. Indeed, some will not find the name "meningorachidian phlebitis" fully acceptable and will raise the question whether the pathologic picture which it denotes is not just one of the pathologic features which characterize an inflammatory disease of the epidural space, the alterations in the epidural plexus of veins being mainly a secondary reaction to a more basic pathologic process.

All are familiar with the observations of Mixter, Browder and Cohen, who reported on a fairly large group of epidural inflammations, some of which were in the nature of granulomatous changes and others of a more frank suppurative process. Browder and others have expressed the view that the suppurative and the nonsuppurative inflammations in the epidural space are usually secondary to an osteomyelitic process in adjacent portions of the vertebral column. Others are of the opinion that vessels in the epidural fat are the seat of a metastatic infectious process. There is a third possibility, and this would be in line with Dr. Fay's idea, that infection of venous channels communicating with branches of the venous plexus in the epidural space may bring about the extension of the inflammatory process to that space.

It is not infrequent that a purulent process in the soft tissue about the spinal column, such as a furuncle, may transmit the infection into the spinal canal by way of venous branches communicating similarly with the veins in the epidural space and in this fashion cause what Fay would call meningorachidian phlebitis. In

this connection it is highly significant that in the slides shown here the pathologic changes in the blood vessels were in excess of those in the surrounding dural tissue.

It seems to me, however, that meningorachidian phlebitis is only an expression of an extension of a suppurative process, primary in an adjacent soft or bony tissue, or else is the result of metastasis from a remote focus of suppuration.

Dr. Frank Konzelmann, Philadelphia: The pathologic picture varies with the age of the infectious process. Some cases were seen in which it seems to have been particularly early. In these the small blood spaces were dilated and tortuous; many were jammed with red blood cells, though actual thrombosis in these blood spaces could not be demonstrated. The smaller venules observed showed either actual thrombosis or an early inflammatory change in the wall of the vessel. These early changes were characterized by collections of polymorphonuclear leukocytes. Still other venules were observed in which the thrombi had undergone organization and were represented by fibrous masses. In some cases recanalization of the thrombus was seen. In the cases in which the process was more advanced fewer polymorphonuclear leukocytes were encountered. Large mononuclear leukocytes, plasma cells and lymphocytes were present. The cells occurred in great numbers, and there was a tendency for these cells to collect in clumps, sometimes apart by themselves and sometimes in the vicinity of small arterioles or venules. Frequently in these more advanced stages there was active proliferation of fibroblasts. The dilatation and tortuosity of vessels were not so apparent in the advanced as in the earlier stages.

Anatomic Factors Influencing Neural Integration: The Pathologist Looks at Mental Disease. Dr. Helena E. Riggs and Dr. John O. Griffiths, Philadelphia.

Similarity of the reactions during lack of oxygen and those present in the psychoses suggests a relationship between cerebral anoxia and mental disease. On the basis of this premise we have analyzed the postmortem observations in 290 cases in which symptoms of acute disturbances in psychic function developed. Since the study is concerned with the evaluation of pathologic states predisposing to cerebral anoxia, no attempt has been made at classification along psychiatric lines; in particular, no distinction has been drawn between conditions of primary psychogenic origin and those secondary to somatic disease.

Classification on this basis demonstrated that, regardless of the cause of the primary disease, there was present in all cases some form of circulatory disturbance as a basis for potential cerebral anoxia. In 37 per cent of cases this was due to quantitative alterations in circulation incident to cardiocirculatory disease; in 39 per cent metabolic disturbances, infection or anemia accounted for qualitative changes in circulatory efficiency, and in 24 per cent, increased intracranial pressure provided a local basis for circulatory disorders. However, the absence of mental disturbances in a control group of 173 cases in which there were similar pathologic conditions demonstrates that the circulatory disturbance of somatic disease does not necessarily produce a sufficient degree of cerebral anoxia per se to precipitate psychic dysfunction.

The frequency of anomalies of the cerebral vascular tree in the psychotic group (psychotic group, 94 per cent; nonpsychotic group, 69 per cent), however, suggests that alterations in cerebral hemodynamic relations resulting from such malformations may so intensify the cerebral effects of the stagnation anoxia that disturbances of psychic integration occur. It has been found from study of 1,300 cases that all anomalies of the circle of Willis can be classified on the basis of failure of the entire circle, or one or more of the primitive stem vessels, to develop to normal adult size. Ontogenic development progresses to the establishment of the normal primate pattern, but either growth of the entire tree is retarded, with consequent hypoplasia of a normally formed circle, or defective growth of one of the primitive stem vessels results in abnormal development of normal anastomoses, with apparent retention of a phylogenetically inferior pattern.

Normal structural development of the brain in the presence of a hypoplastic or phylogenetically retarded cerebral vascular system implies a reduced margin of cerebral vascular reserve, especially in the areas of more recent evolutionary growth. Hydraulic compensation necessary to maintain dynamic circulation in such anomalous circles is obtained only at the expense of reduced circulation in the entire cerebral vascular system. Since the pressure and volume of blood entering the brain from each internal carotid artery and from the basilar artery are approximately the same, the increased resistance resulting from focal hypoplasia in one portion of the circle must be balanced by increasing the field of supply in another part of the circuit. As a result, in a person with an anomalous circle of Willis cerebral circulation, at any given level of systemic blood pressure, is less effective than that in a person with a normal cerebral vascular tree and alterations in peripheral circulation, too small to influence blood flow in the normal circle, may produce definite cerebral circulatory insufficiency. Thus, during alterations of systemic circulation incident to somatic disease, cerebral anoxia sufficient to produce psychic disorders occurs in 23 per cent of persons with a normally formed cerebral vascular tree and in 82 per cent of those whose margin of cerebral circulatory reserve has been reduced through anomalies of the circle of Willis.

Chemical Factors Influencing Acute Psychoses. Dr. S. De W. Ludlum, Philadelphia.

The figures presented here exhibit a striking relation between the forces of heredity and immunity and the mind.

If the total and fractionated proteins in the blood serum of acutely psychotic patients are measured in many hundreds of cases, the following facts appear:

The patients who show predominance of albumin are those who are asthenic, do not exhibit immunity to the diseases of childhood and are prone to the early development of dementia. They do not have a normal amount of globulin. In 1 case the total proteins measured 6.5 Gm. per hundred cubic centimeters, of which albumin constituted 73 per cent, pseudoglobulin 18 per cent and euglobulin 9 per cent. The normal proportions should be: albumin 60 per cent, pseudoglobulin 20 per cent and euglobulin 20 per cent.

Immunologically as well as mentally these persons are nonproductive. When they have infections they do not react to them.

The reverse is seen in acutely psychotic persons in whom the globulins, either pseudoglobulin or euglobulin, are predominant, the type of globulin depending on whether the patient is reacting to poisons or to antigens. In a typical case the total proteins measured 8.25 Gm., of which albumin constituted 53 per cent, pseudoglobulin 20 per cent and euglobulin 27 per cent. Such persons are hyperactive mentally, are apt to be hallucinated and react in the immunologic sense with production of euglobulin. Physiologically, they appear toxic.

It would seem, therefore, that patients with mental disease may be divided into two classes, the line being drawn on the basis of the immunologic state, that the equipment of the body to resist disease through the serum is correlated with the function and resistance of the mind and that there is a kinship between the immunologic classification and the psychologic differentiation of introverts and extroverts, the pathologic distinction between regressive and hypercompensatory types and the constitutional division of schizoid and cycloid personalities.

In all my statistical studies, based now on over 1,500 patients, this chemical comparability holds true, and it suggests in patients who show predominance of albumin the lack of an organizer molecule and in patients who are hyperactive the excess of an organizer molecule. The next step, therefore, in the elucidation of psychiatric states is expert chemical work on the essential molecule in the proteins of the blood serum. This element represents a force closely allied to the chemistry of immunity.

It is to be noted that Zinsser said that a child is born with a marked predominance of albumin and that antibodies and globulins appear much later. It would seem that in some cases the globulin fraction never adequately develops.

Something has been written on the effects of the ingestion of the colostrum on the fractionization of protein (Jameson, E., and Alvarez-Tostado, C.: *J. Physiol. Chem.* **43**:1165, 1939), and the subject has been given practical significance by Wade Brown, who produced acquired heredity in experiments on rabbits.

According to my statistics, the osmotic pressure was normal in 16 per cent of cases. In 98 per cent of these cases some other physicochemical characteristic was abnormal. This, with the developmental defect of vessels in 94 per cent of cases, warrants the anatomicophysiologic approach to degenerative nervous diseases, such as the psychoses.

In cases in which albumin is predominant there has always been observed a high osmotic pressure and a low hydrostatic pressure, providing a basis for disequilibrium. The observation of physical-chemical discrepancies in 98 per cent of cases and anatomic defects in the blood vessels in 94 per cent of cases, as well as the swelling effects on the brain seen at autopsy, has rendered persistent in my mind the idea that there is a definite pathologic basis for the degenerative nervous diseases.

DISCUSSION ON PAPERS BY DRS. RIGGS AND GRIFFITHS AND DR. LUDLUM

DR. ISRAEL STRAUSS, New York: One must admit that Dr. Ludlum, if his technic is proper, as I presume it is, gives a series of figures which indicate that there is some constitutional difference in certain classes of psychoses, as there is in other diseases. What conclusions one can draw from the facts is open to judgment. Whether one can go as far as Dr. Ludlum does I do not know. For a number of years he has been engaged in these studies. I know that there has often been a great deal of skepticism expressed, not as to the correctness of his figures but as to his conclusions. Today I feel that possibly in these studies Dr. Ludlum is blazing a pathway which may eventually prove of value in investigating the cause and progress of mental disease.

DR. S. DE W. LUDLUM, Philadelphia: One will not observe cerebral anomalies in all cases; yet the student will invariably ask: "Why are the patients with arthritis not insane?" I contend that what we are doing is consistent with the principles of medicine. Many autopsies performed for the department by Dr. Riggs have revealed a high frequency of "wet" brains. In such cases the osmotic pressures are low. It is worthy to note that the psychotic persons with high osmotic pressures usually did not die; therefore we are unable to say much about their brains.

Effect of Vitamin E on the Muscular Dystrophies. DR. BERNARD J. ALPERS, DR. HERBERT S. GASKILL and DR. A. CANTAROW, Philadelphia.

The first reported production of a nutritional dystrophy was that by Evans and Burr (*J. Biol. Chem.* **76**:273 [Jan.] 1928) in rats suckled by vitamin E—low mothers. Since then a considerable number of experimental studies by workers here and abroad have confirmed this finding, the details of which cannot be discussed now. This nutritional dystrophy can be produced in a wide variety of species when maintained on vitamin E—deficient diet. The disease is characterized by increasing weakness of the hindlimbs, progressing to complete paralysis; the majority of the animals then die of an intercurrent respiratory infection; a few recover spontaneously. This disease can be prevented or cured by the addition of vitamin E to the diet, but the curative value of the vitamin appears to be less than its preventive value. During the acute stage of the disease pathologic studies show hyaline degeneration of the musculature, with replacement by fatty and connective tissue. Some reports indicate that there is involvement of the central nervous system.

The marked similarities in symptoms and pathologic changes between this type of nutritional dystrophy in animals and the muscular dystrophies in man sug-

gested the possibility that vitamin E might have some therapeutic effect in treatment of the latter. Two reports on the use of vitamin E in clinical material have appeared since this study was begun. Bicknell (*Lancet* **1**:10 [Jan. 6] 1940) found vitamin E effective in a number of cases of progressive muscular dystrophy and in 2 of 4 cases of amyotrophic lateral sclerosis. Wechsler (Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols [Vitamin E], *J. A. M. A.* **114**:948 [March 16] 1940) has reported successful treatment in 2 cases of amyotrophic lateral sclerosis.

The present study was begun last summer to determine the effectiveness of vitamin E in cases of progressive muscular dystrophy. The primary aim of the study was to evaluate alterations in muscle metabolism as indicated by changes in creatine and creatinine metabolism while the patient was under treatment. The symptomatic response of the patient was regarded as secondary and is only incidentally reported on. The patients, therefore, were admitted to the hospital and, after the preliminary studies had been completed, were placed on weighed diets containing a constant minimum amount of protein. After the patient's metabolism had become adjusted to the new diet, daily twenty-four hour specimens of urine were sent to the laboratory for determinations of creatine and creatinine. After a control period of about two weeks, the patients were given wheat germ oil, 1 fluidrachm (3.7 cc.) twice a day. As yet we have not used alpha tocopherol in these studies. During the period of treatment the clinical progress of the patients was evaluated, together with alterations in the creatine and creatinine excretion.

The first 2 patients were a brother and a sister, aged 17 and 22, respectively; both have been receiving vitamin E for over eight months, without any clinical improvement. The 2 other patients were studied more extensively and form the basis of this report. Patient 3, a boy aged 4, showed the characteristic features of progressive muscular dystrophy. Although there were times during the period of treatment when the creatine excretion was significantly lowered, this decrease was not sustained. He felt much better subjectively, but there was little objective evidence for this. Patient 4, a youth aged 19, had a typical form of the disease and showed definite improvement under treatment. The creatine output during the period of medication was constantly lower than that in the control period, except on two occasions when he had a mild infection of the upper respiratory tract with low grade fever. In addition, he showed marked clinical improvement.

From so few cases no definite conclusions can be drawn, but it at least encourages one to hope that some patients with progressive muscular dystrophy may be improved by vitamin E therapy. This improvement may be secondary to altered muscle physiology, as evidenced by the change in creatine and creatinine metabolism, seen particularly in patient 4.

DISCUSSION

DR. ISRAEL S. WECHSLER, New York: My own experience deals more with amyotrophic lateral sclerosis than with the dystrophies. Altogether, I have had 4 patients with dystrophy. Of these, 1 seemed to respond fairly well; I am not sure that the other 3 have shown any improvement.

The experience which I gathered from the treatment of amyotrophic lateral sclerosis may be applied in some measure to the dystrophies. What I have done so far is to saturate the patients with vitamin E, and since there is some evidence that vitamin B_1 has to do with atrophy, I have also prescribed the whole B complex. I have also added bile salts, since from experience with vitamin K, which is also fat soluble, I thought that absorption of the vitamin E would be facilitated. So far the results in cases of amyotrophic lateral sclerosis have been almost startling. Of 30 patients, not 1 died. Several have recovered completely. A number showed varying degrees of recovery. I can now state with assurance that the process can be arrested and that the degree of recovery is in direct ratio to the extent and duration of the disease process. I think that I can also state that the absence of vitamin E is a specific cause and that the administration of vitamin E will bring about recovery. There is undoubtedly an x factor in the gastrointestinal tract which interferes with absorption.

Dystrophies are not quite comparable. To begin with, there must be a genetic factor in addition to privation of vitamin E. The question is why there is malabsorption of vitamin E if that is the x factor. It may be recalled that Bicknell gave the wheat germ powder, and not the oil or the tocopherol. Whether the good results are best obtained with the powder I do not know. While there is some evidence that absence of vitamin E operates in the dystrophies, the recent paper by Antopol on good results of treatment with vitamin B_6 is of considerable importance. It seems to me worth while, therefore, to try other vitamins in addition to the tocopherol and the whole wheat germ oil. Another question is whether injection of tocopherol in oil intramuscularly is superior to the administration of tocopherol by mouth. There is evidence that vitamin E operates best when absorbed through the gastrointestinal tract, but I should add that in 2 cases the injections seemed to be effective when the oral administration did not. In all other cases the oral administration was adequate.

DR. BERNARD J. ALPERS, Philadelphia: Dr. Wechsler is undoubtedly right in stating that for purposes of treatment one must use not only the wheat germ oil but the residue as well. Since we were interested in determining the exact status of vitamin E in its effect on muscle function in the dystrophies, we used only the wheat germ oil, because the residue contains other vitamins which might have affected our results.

Operable Lesions of the Spinal Cord: Analysis of Sixty Cases Which Occurred in the Past Five Years. DR. JOSEPH C. YASKIN and DR. ROBERT A. GROFF, Philadelphia.

We are presenting a résumé of 60 cases of lesions of the spinal cord in which operations were performed within the past five years, most of them within the past two years. Study of this small group of cases revealed some facts, which were deemed of sufficient interest to present at this meeting.

The types of lesions and the frequency with which they occurred in these 60 cases were as follows: meningioma, 11 cases; neurofibroma, 9; glioma-syringomyelia, 9; chordoma, 1; perithelioma, 2; hemangioma, 2, and Paget's disease, 2.

In 52 per cent of the cases the prognosis from the functional standpoint was definitely favorable. Some of the patients with tumors of the spinal cord were completely paralyzed on admission to the hospital. One patient had complete quadriplegia with serious respiratory difficulties and yet made a complete recovery after the removal of a neurofibroma in the cervical region. Two patients had marked paraplegia in flexion. One patient with a meningioma was bedridden for three years and yet made a satisfactory functional recovery.

In a second group (12 per cent of cases), including those of sarcoma and arachnoiditis, the prognosis was fair.

In a third group (36 per cent of cases) in which the prognosis was definitely poor glioma-syringomyelia occurred in 9 cases, chordoma in 1 case, perithelioma in 2 cases, hemangioma in 2 cases, Paget's disease in 2 cases, sacral tumors in 4 cases and carcinoma in 4 cases.

We desire to stress the following points:

1. Many of these operable lesions were originally considered as degenerative lesions, and much valuable time was lost. The medical profession is not fully conscious of the frequency of operable conditions.

2. Pain in the back is a fairly constant symptom of operable lesions of the spinal cord (tumors, herniation of the nucleus pulposus and hypertrophied ligamentum flavum). Backaches are often treated by orthopedists for too long a period before being given the benefit of neurologic study.

3. Roentgen studies with the aid of a contrast medium should be resorted to in all doubtful cases, but only after a careful evaluation of the historical data and of the neurologic and orthopedic abnormalities.

4. Iodized poppy seed oil is at present the best contrast medium. It is harmless, reliable with good technic, permits the finding of small lesions (for instance, a neurofibroma 4 mm. in the largest diameter arising from the right fourth lumbar root) and makes for smaller laminectomies.

5. Complete paralysis is in itself not a contraindication to operative procedures. The mortality from laminectomy has been markedly reduced, only 1 death having occurred in the present series.

DISCUSSION

DR. BYRON STOOKEY, New York: Dr. Yaskin and Dr. Groff have emphasized the need for early diagnosis and neurosurgical intervention in cases of such lesions of the spinal cord. I agree that the neurologic findings may not always be sufficient to distinguish between degenerative diseases and new growths, but special examinations can be utilized to make satisfactory differentiations; certainly, iodized oil will show an obstructive lesion. In addition to the manometric examination, the roentgenogram may reveal the relative sizes of the vertebrae and the degree of atrophy or separation of the pedicles. As to the value of iodized oil, I agree that it has an important place in the case in which there remains doubt as to the nature of the lesion or in which the level cannot otherwise be determined.

DR. JOSEPH C. YASKIN, Philadelphia: I should like to emphasize the fact that we are not using iodized oil in every case in which a space-taking lesion of the cord is suspected. However, frequently an early diagnosis of such lesion cannot be made without a contrast medium. Such is frequently the case with protruded intervertebral disk. Also, slowly progressive, extramedullary tumors of the cord may be accompanied by much pain without disturbances of subarachnoid hydrodynamics or any other evidence of compression of the cord. In such cases oil studies are justifiable for an early diagnosis.

The Neurophysiologic Basis of the Parkinson Tremor. DR. MELVIN W. THORNER, Philadelphia.

This is a study of the involuntary tremor movements found in the syndrome first described by James Parkinson, in 1817. The study utilizes mainly clinical material, with some correlative animal experiments. Electromyographic recordings of the muscle contractions show that the individual fibers in a tremulous muscle contract in groups at regular intervals. No contractile muscle activity occurs between these groupings. When simultaneous recordings are made of antagonistic muscles engaged in tremor, the groups alternate in their contractile periods.

The tremor response may be initiated by a stretch reflex in the patient with parkinsonism. This tremor oscillation is not seen after the stretch reflex in normal human subjects or animals or in spinal cats. Since the stretch reflex requires intact dorsal roots, these structures are probably necessary for the occurrence of parkinsonian tremor. The tremor response to a stretch reflex may be regarded as an underdamped oscillation.

In many essential respects the oscillatory tremor in parkinsonism behaves in a manner common to oscillatory activity in general. Its rate may be modified by varying such factors as mass, resistance and compliance, as may oscillating systems in general—the pendulum for example. Like sustained oscillating systems elsewhere, some "feed back" mechanism is necessary. This is found to reside in the dorsal roots and the long projection tracts of the spinal cord. The latter are shown to exist by dorsal ramisectomies (both in human beings and in experimental animals) and by the clinical observation that parkinsonian tremor is stopped homolaterally within the onset of hemiplegia.

Contractile activity of muscles in parkinsonism consists of three types: (1) voluntary, the electromyographic picture of which is essentially like that of the healthy person; (2) increase in tone, in which nonsynchronized discharges appear,

and (3) synchronized discharges or tremors, which may represent an unstable, underdamped version of type 2. None of these ever appears at a time when the others are present.

Parkinsonian tremor is viewed as an underdamped oscillating system which is sustained by feed-back mechanisms. It appears in the nervous system in which elements of the normal damping mechanism (the extrapyramidal system) have been injured by disease. It conforms to the laws applying to oscillating systems in general, and predictions concerning it may be derived from consideration of these laws.

DISCUSSION

DR. TRACY J. PUTNAM, New York: Dr. Thorner's paper seems to me an excellent illustration of the value of electromyography in the comprehension of the physiology of abnormal, as well as of normal, muscle management. The work which Dr. Hoefer and I reported at the American Neurological Association last year was in general agreement with his results. We were particularly interested in the manner of discharge of motor units. In normal voluntary contraction they discharge asynchronously and at varying rates. This is the situation also in athetosis and chorea. In "spasticity" and parkinsonian tremor, on the contrary, there is a high degree of synchronization.

I am sure that Dr. Thorner is aware that the clinical observation made by Parkinson has been confirmed by recent surgical experiences. Interruption of the pyramidal tract, either by an excision of the motor cortex or by section of the tract in the spinal cord, greatly reduces tremor; the latter operation appears to cause less disability than the former. The results of section of posterior roots have been reported by Davis and by Foerster; it appears to decrease the rigidity and to modify the rate of tremor, but the extent of the tremor is little changed. Section of the posterior column has been reported by Puusepp and by Rizzatti and Moreno; it also decreases rigidity, but does not affect tremor.

Just how all these diverse pieces of evidence can be fitted together I do not at present clearly see, but there must be some explanation for them.

DR. MELVIN W. THORNER, Philadelphia: I should like to thank Dr. Putnam for his considered discussion of this paper.

The neurophysiologic principles which are involved in any explanation of the parkinsonian tremor become complicated indeed; however, certain practical results may be held forth, even from incomplete knowledge of this clinical phenomenon: These include the various operative procedures on the pyramidal tract and the extrapyramidal tracts. Dr. Groff and I have been particularly interested in the practical significance of the "feed-back" mechanisms, which involve the dorsal roots. In several patients in whom we partially excised these structures a considerable degree of improvement was noted.

Perhaps the real importance of these questions is a consideration of neurophysiologic phenomena in mechanical terms.

Treatment of Migraine with Vitamin B_1: Résumé of One Year's Experience. DR. HAROLD D. PALMER, Philadelphia.

The migraine episode is considered an entity made up of three phases: (1) the prodromal stage of toxic accumulation; (2) the resulting imbalance of the sympathetic nervous system, leading to cerebral vascular dilatation (headache), and (3) the stage of elimination or recovery.

This view of migraine, formulated after a ten year study of the problem at the Institute of the Pennsylvania Hospital, led to the idea that there might be in persons subject to migraine attacks either a total body toxemia of metabolic origin or the absence or deficiency of an enzyme essential to normal tissue metabolism. In view of recent investigations showing the importance to normal tissue metabolism of vitamin B_1 and of Peters work (*Lancet* **1**:1161 [May 23] 1936) emphasizing the loss of equilibrium of the nervous system in acute vitamin B_1 deficiency, a study was undertaken of the effects of administration of vitamin B_1 in a number

of cases of severe migraine. The first results of the treatment of 11 patients with severe migraine by means of frequent intramuscular injections of large doses of vitamin B_1 were encouraging. Since that time the scope of the study has been enlarged, through a grant from the New York Foundation, so that at present more than 50 patients are under treatment, and of this number 48 have received intensive therapy for periods of seven months to one year.

Method of Treatment.—Treatment consists of daily intramuscular injections of 30 to 100 mg. of thiamine hydrochloride for one or two months. The preparation used contains 60 mg. of synthetic vitamin B_1 (thiamine hydrochloride) per cubic centimeter. In moderately severe conditions the length of intensive treatment may be shortened, but in the more severe reactions the high dosage may have to be continued for several months. When freedom from attacks is obtained, the frequency of administration may be reduced gradually. In most cases the reduction is made as follows: 60 to 100 mg. is given three times a week for one month, then 60 to 100 mg. twice a week for one month and then 100 mg. once a week for an indefinite period. The solution of thiamine hydrochloride may be given intravenously, but this technic seems to have no advantage over the intramuscular method. If it is given intravenously, a more dilute solution must be used, the concentration being not greater than 10 mg. per cubic centimeter. In an attempt to interrupt an impending attack, successful use has been made, without any ill effect, of as much as 150 to 180 mg. given intramuscularly.

All patients undergo physical and neurologic examinations, and when indicated laboratory studies are made. Electroencephalographic studies are a routine part of the pretreatment investigation.

During the entire course of treatment the patient is requested to take orally one of the preparations of the vitamin B complex. Various forms have been used, and the average daily oral dose has been 750 international units of vitamin B_1, 1,000 Sherman-Bourquin units of vitamin G (about 3 mg. of riboflavin), and 6 mg. of nicotinic acid. In 6 cases 50 mg. doses of nicotinic acid have been given orally two or three times daily during the entire period of vitamin B_1 therapy, but the response in these cases has not differed significantly from the response in the cases in which the total B complex preparations were given. During a test period of six months, 7 patients have been given nicotinic acid alone in oral doses of 50 to 150 mg. daily, and some benefit has been reported. Some patients, however, have expressed the belief that nicotinic acid taken at the time of a migraine episode aggravated the symptoms. Others have reported that approaching headaches have apparently been aborted by the use of the large oral doses of nicotinic acid. Further observations on various combinations of nicotinic acid and vitamin B_1 are in progress.

Results.—Twenty-three of the 48 patients treated have been completely relieved of migraine attacks. In this group are a number of patients whose headache occurred almost daily and who required as many as twenty to thirty hypodermic doses of ergotamine tartrate each month in order to control the disorder. Several of these patients had suffered many symptoms of ergotism. Of the 23 patients who were completely relieved, 12 have been able to discontinue treatment after an average of less than four months of administration of vitamin B_1. Only 1 has had any recurrences, and these have been of mild character.

Fourteen of the 48 patients can be classified at this time as "responding to treatment" in that they have experienced substantial improvement in reduced frequency and severity of headache. The ratio of improvement in this group is better than 10 to 1. One patient has been receiving 60 mg. of thiamine hydrochloride weekly for more than one year, and, although there is an occasional headache, the treatment has enabled her to resume her occupation, which near invalidism resulting from the migraine had previously forced her to abandon.

Four of the 48 patients have failed to obtain relief from the chief problem of headache, but have gained weight and have shown general physical improvement.

Four patients require special mention. One proved to have an allergic sensitivity to thiamine hydrochloride. Another, who had been receiving ten to twenty hypodermic doses of ergotamine tartrate per month over a period of years, reported

that thiamine hydrochloride produced aggravation of the peripheral vascular pains which she had recently experienced with each dose of ergotamine tartrate. One patient with severe migraine experienced complete relief for sixteen weeks while receiving thiamine hydrochloride and had no recurrence of headache until six weeks after stopping the medication. The recurring headaches have failed to respond to further vitamin B_1 therapy. One patient has had complete relief from headache but suffers various manifestations of migraine equivalent.

In the 48 cases studied, doses of 120 to 180 mg. of thiamine hydrochloride were given successfully for the relief of acute attacks. In more than 150 instances (70 per cent) the attack was terminated within one to three hours. In only 58.8 per cent of these cases had relief previously been obtained from the use of ergotamine tartrate.

DISCUSSION

Dr. Mary E. O'Sullivan, New York: I agree with Dr. Palmer that the pathophysiologic basis of migraine is a diffuse process and is probably intimately connected with changes in the vascular system. For many years Dr. Kennedy has believed that edema of neurologic structures is the only pathophysiologic process that could explain all the phenomena of migraine. By means of capillaroscopy, we have observed an increase of fluid in the cutaneous tissue spaces of the entire body, existing to a much greater extent on the side of the unilateral headache.

I also agree with Dr. Palmer that the hereditary link between migraine and epilepsy has been greatly overrated. In only 0.8 per cent of our series of approximately 300 cases was there a history of epilepsy in either the offspring or the antecedents.

I regret that I have no experience in use of the dosage of thiamine hydrochloride employed by Dr. Palmer. I know of 1 patient who after daily ingestion of brewers' yeast has been symptom free for over five years, except during intervals in which the medication was discontinued. In other patients the brewers' yeast has seemed to alleviate the neuralgic type of headache, but has been ineffective in preventing the classic attacks.

In treating a syndrome such as migraine, I believe it is unwise to recommend a curative therapy without an attempt to classify the patients etiologically. There is no doubt that some forms of migraine are precipitated by endocrine dysfunction and can be cured by specific endocrine therapy. There are also attacks of allergic migraine which are completely abolished by such measures as elimination diets. I do not believe that one cure for all these etiologic factors will be found. Another substance, such as ergotamine may be found, that will be of temporary benefit to 90 per cent of the patients, but I do not believe that such a substance will permanently change the pathologic process in all types of migraine.

I was amazed by Dr. Palmer's experience with ergotamine tartrate. The effectiveness of this medication has been well established by several clinics and over a period of seven years.

Because of the character of the migraine syndrome and the confusion in the literature on the treatment of this condition, we have established a therapeutic routine which we believe to be indispensable in the evaluation of any therapy.

For a month after admission to our clinic a patient is initiated with placebos identical in form with the medicament which is later to be tested in actual treatment. It is amazing how many patients are relieved of their attacks in this early period before therapy is begun.

Dr. Palmer's results have been excellent. I believe it important to continue with this experiment. Any further aid in the therapy of the migraine syndrome is certainly to be encouraged.

Dr. Harold D. Palmer, Philadelphia: I have followed with great interest the work in the clinic of Dr. Kennedy and Dr. O'Sullivan, and it is a pleasure to have Dr. O'Sullivan's discussion of my brief report.

The demonstration of unilateral edema is of great value, and it may be that one of the most important effects of vitamin B_1 in large doses has to do with

the reduction or elimination of this edema. The action of vitamin B_1 in alcoholic delirium and other states in which cerebral edema is intense would seem to support such a concept. Also, one of the prompt effects of vitamin B_1 administration in my patients with migraine is free diuresis.

The 58.8 per cent success with ergotamine tartrate in this group of patients is low as compared with that reported by other investigators. However, it must be remembered that ergotamine tartrate now has very general use and that when some new method appears to give promise the applicants for the new therapy will be made up largely of those who have failed to find sufficient help from the use of ergotamine tartrate, allergic management, endocrine therapy and other methods. In the recent past I have attempted to relieve some of the toxic accompaniments of administration of ergotamine tartrate by giving an extract of belladonna leaf hypodermically. This method seems to offer some promise.

It is certain that not all patients with migraine will respond to vitamin B_1 therapy, but a very encouraging proportion of those treated so far have been benefited. Those failing to respond are to be studied and treated by methods now in the stage of further development.

AMERICAN ASSOCIATION OF NEUROPATHOLOGISTS

STANLEY COBB, M.D., *Presiding*

Annual Meeting, Rye, N. Y., June 6, 1940

Recklinghausen's Disease Associated with Glioblastoma Multiforme and Ganglioneuroma of the Central Nervous System: Report of a Case.

DR. CHARLES DAVISON, New York.

It is well known that Recklinghausen's disease may be associated with other neoplasms of the central nervous system, such as multiple meningiomas, tuberous sclerosis, Lindau's disease, spongioblastoma polare, angiomas and occasionally glioblastoma multiforme. A review of the literature disclosed only 1 case (that of Roger and Alliez) in which the cerebral tumor was a glioblastoma multiforme. Cases in which the condition was associated with ganglioneuromas had not previously been reported, as far as could be determined.

A woman aged 32 at the age of 16 had noticed nodules on the right side of the arms, which gradually spread over the entire body. They were elevated, bluish white and painless. At the age of 31, in January 1935, she experienced occasional headaches, increasing in severity and frequency. In February 1935 she saw double, and an internal squint developed in the left eye. In June 1935 there appeared generalized convulsions of the entire body, with frothing at the mouth, biting of the tongue, loss of consciousness and incontinence of urine. One cousin had epilepsy. The patient's youngest child had nodules over the body similar to those of the mother.

Examination disclosed numerous neurofibromas, generalized hypotonia, ataxia in the heel to knee test and other signs of cerebellar lesion on the left side. There was right flaccid hemiplegia with hyperreflexia and a Babinski toe sign on the same side. The abdominal reflexes were absent. Because of the patient's mental condition, a careful sensory examination could not be done. There were marked bilateral papilledema, with hemorrhages in both fundi, and total blindness in the left eye. Both external rectus muscles were weak. There were left internal strabismus and weakness of the lower right side of the face. Grasping and groping movements of the left hand were present. The patient was confused, distracted and disoriented. Memory was poor for recent and remote events.

A ventriculogram indicated the presence of two tumors, a large one in the left hemisphere along the sylvian fissure and another in the left occipital lobe.

At operation, performed on April 5, 1936, a glioblastoma multiforme was found in the left frontotemporoparietal region.

Autopsy revealed a tumor 4.5 by 2.5 cm. in the left frontotemporoparietal region and a swelling of the left side of the medulla oblongata.

On microscopic examination the tumors of the skin had the typical appearance of neurofibromas. The tumor in the region of the left frontotemporoparietal region was a glioblastoma multiforme, while the one in the left side of the medulla oblongata was a ganglioneuroma.

Giant Cells in Some Forms of Acute Meningitis, Including the Coccidioid Types. DR. G. B. HASSIN, Chicago.

The pathologic picture of meningitis strikes one by its monotony, especially on superficial examination. Lymphocytes and plasma cells, sometimes mixed with polyblasts or polymorphonuclears, depending on the type of meningitis, are the common features. Occasionally, apparently ordinary meningitis hides something unusual among the masses of hematogenous elements, for instance, a Trichina embryo. A Trichina embryo produces a reaction in the brain tissues in the form of cell accumulations or nodules. These enclose the parasite, which usually appears granular, as if eaten away by the masses of glia cells which form the nodule.

In some types of meningitis the pathologic picture is somewhat enlivened by the presence of giant cells. Giant cells are not typical of any kind of meningitis, for they occur in meningitis associated with syphilis, tuberculosis, torulosis, Hodgkin's disease and other conditions, of which that caused by infestation with Coccidioides immitis deserves especial attention. In this form the usual inflammatory cells seen in meningitis are mixed with immense masses of giant cells, which appear in some areas in pure culture. Each giant cell invariably harbors the parasite or its numerous immature forms, the sporozoids; it also contains immense masses of nuclei, as many as 100 in some instances. In their size and wealth of nuclei the giant cells in coccidioid meningitis are analogous to the giant cells which occur in the brain or spinal cord in the presence of a foreign body, being a manifestation of a peculiar tissue reaction. This differs from a reaction produced by the presence of a Trichina parasite or a hemorrhagic focus. In the latter case the reacting cells are, as in meningitis due to Trichina, not giant cells but mobile histiocytes (macrophages) which pick up granules of blood pigment; in trichiniasis the histiocytes devour the digestible parasite, while in coccidioid meningitis the giant cells are called on to protect the tissues against the parasite by merely enveloping them. These giant cells are similar to the well known foreign body giant cells, which occur in the presence of a foreign body in the brain tissues and cannot be digested or rendered harmless by ordinary phagocytes. They denote a dangerous condition—the presence of an exogenous, undigestible element.

DISCUSSION

DR. R. MORRISON, Boston: Dr. Hassin points out that both types of cells are engaged in active phagocytosis, the macrophages containing blood pigment and the giant cells containing spores. I should like to ask whether he implies that the cells are related, that is, whether he considers the giant cell to be a multinucleated gitter cell.

DR. G. B. HASSIN, Chicago: Possibly one can find a mitotic figure, but not a multinucleated cell. The giant cells were packed with sporozoids or nuclei or both and were multinuclear. Gitter cells are mononuclear formations, though they may exhibit mitotic figures.

Cerebral Histopathologic Changes Associated with Anaphylactic Reactions. DR. G. A. JERVIS, DR. A. FERRARO, DR. L. KOPELOFF and DR. N. KOPELOFF, New York.

This paper will be published in full in a future issue of the ARCHIVES.

Arsenic as a Possible Cause of Subacute Encephalomyelitis: A Correlation of Chemical, Clinical and Histologic Observations. Dr. A. D. Ecker and Dr. J. W. Kernohan, Rochester, Minn.

This paper was published in full in the January 1941 issue of the Archives (**45**:24-43, 1941).

DISCUSSION

Dr. F. H. Lewy, Philadelphia: I should like to ask the authors about the relation of the degree of encephalomyelitis in their patients and the amount of arsenic found in the central nervous system. Reports in the literature seem to indicate that no such relation exists in cases of lead encephalopathy.

Dr. A. D. Ecker, Rochester, Minn.: Whenever more than 0.1 mg. of arsenic per hundred grams of brain tissue was found there was invariably profound alteration of the tissue, demonstrable under the microscope. The arsenic is not always distributed homogeneously throughout the substance of the brain. This was pointed out first by Osterberg and Kernohan, who found a greater concentration of arsenic in the white matter than in the gray matter of the brain in their 4 cases of pericapillary hemorrhage. In the cases of encephalitis, as in those of hemorrhage, if arsenic was present in any given brain, it was almost always found in maximal concentration at the site of greatest pathologic change. However, the actual amount of arsenic in the different brains of the encephalitis series did not correspond at all to the severity of the pathologic change. The general autopsy did not reveal disease of other organs.

Primary Encephalitis in Goats Due to Bacterial (Listerella) Infection. Dr. L. S. King, Princeton, N. J.

In a series of 9 goats spontaneous encephalitis associated with Listerella infection was observed.

Pathologically, the lesions were essentially restricted to the brain stem, especially the medulla and the spinal cord. The peripheral nerves and ganglia were inconstantly affected. There was associated meningitis.

The primary parenchymal lesion is a circumscribed focal collection of mononuclear cells (with or without admixture of a few neurophilic leukocytes) in close relation to a blood vessel. The infection is fulminating. Diffuse tissue infiltration may supervene, sometimes with the formation of small abscesses, but these are secondary and late phenomena. The blood vessels show marked degenerative changes, coupled with cellular infiltration of the walls and adventitia. Bacteria can frequently be demonstrated histologically in the parenchymal lesions. Nerve cells may be destroyed, but there is relatively little tissue necrosis.

Pathologic Changes in the Ligamentum Flavum. Dr. F. H. Lewy and Dr. R. A. Groff, Philadelphia.

The physiologic mechanism of the clinical syndrome of the protruded nucleus pulposus is not sufficiently explained by the presence of changes in the disk. The same symptom complex occurs in the absence of a protruded disk; the appearance of repeated attacks of paroxysmal pain with pain-free intervals for years and the preponderance of pain over weakness in the presence of a mass lesion pressing in an anteroposterior direction require explanation. Bands and patches of degeneration are frequently observed in so-called normal ligaments in which the elastic fibers fail to stain and in which the perifibrillary connective tissue sheath has increased in size. Yet close inspection seems to indicate that the elastic fibrils in these areas, although unstainable, are not destroyed. We venture to suggest that these changes represent the normal wear and tear of the ligaments and are not manifestations of disease. The pathologic changes in the ligaments of patients operated on for herniated disk, whether or not such a disk was found, may be divided into three groups: (1) physical ruptures of the elastic fibrils in consequence of trauma with formation of a firm connective tissue scar; (2) diffuse, perivascular degeneration of the elastic tissue, possibly of inflammatory nature,

with formation of a loose, indolent scar, and (3) a hypertrophic ligament at the level of the lesion. This hypertrophic ligament shows mild edema and swelling of the elastic fibrils with thickening of the perifibrillary and interfibrillary connective tissue. However, seemingly normal ligaments from the same patient several segments below the original level which were removed for a control study showed the severest degree of degeneration. Here, the majority of elastic fibrils had disappeared and were replaced by connective tissue, which in its turn had broken down to form cystic cavities. The questions are raised whether a hypertrophic ligament may constrict the posterior root, thus producing pain, whether the thinned and degenerated ligament may be caught momentarily between the vertebral arches and thus lead to the repeated attacks of pain and, finally, whether a primary inflammatory disease of the ligaments occurs.

DISCUSSION

DR. J. W. KERNOHAN, Rochester, Minn.: Studies on the so-called hypertrophied ligamentum flavum at the Mayo Clinic were carried out by Dr. M. B. Dockerty, in the section on surgical pathology. Dr. Dockerty studied lumbar ligaments taken at operation in 50 consecutive cases in which a diagnosis of protruded disk and hypertrophied ligamentum flavum had been made. These ligaments were compared with a series of 25 normal control specimens secured at necropsy.

In the pathologic series thickening was observed along with varying grades of fibrous replacement of normal elastic tissue. The average grade of fibrosis was 2 on a basis of 1 to 4, in which 1 indicates minimal and 4 maximal fibrosis. Severe fibrosis always was accompanied by hyaline changes in the walls of nutrient blood vessels. Calcification occasionally was observed, and islands of cartilage were found in several instances. Because the process appears to be one of degeneration and fibrosis, it is proposed that the designation "thickening and fibrosis" be used in place of the rather inaccurate term "hypertrophy."

Meningeal Fibroblastoma with Hyperostosis About the Optic Foramen.

DR. W. L. PENFIELD and DR. G. ODOM, Montreal, Canada.

Meningeal fibroblastomas with hyperostosis of the overlying bone are not uncommon over the vault but are rather rare about the base of the skull.

Mrs. F. W., a white woman aged 49, was admitted to the Montreal Neurological Institute on Jan. 25, 1940 complaining of periodic headache since the age of 6, pain behind the left eye for two years, a recurrent blindspot in the medial portion of the left visual field for the past two years, drooping of the upper eyelid for the last year and failing vision in the left eye for the last two months. The only positive neurologic findings were referable to the left eye. They consisted of slight proptosis, drooping of the upper lid, decreased visual acuity and a central blindspot. Roentgenograms of the skull and optic canal showed increased density of the left anterior clinoid process. This increased density extended as far medially as the midline and a short distance laterally, completely encircling the optic canal.

At the time of operation a reddish tumor, about the size of a walnut, was found situated on the medial end of the lesser wing of the sphenoid bone, completely surrounding the optic foramen and infiltrating about the carotid artery. The bone of the posterior and medial aspects of the roof of the orbit and the medial aspect of the lesser wing of the sphenoid was very dense and thickened.

The microscopic sections proved to be those of a very slow-growing meningeal fibroblastoma, with numerous whorls and psammoma bodies. The tiny pieces of bone which were removed from the extraordinary thickening about the optic foramen contained tumor cells in the haversian canals. In no place were the tumor cells in direct contact with the bone, there always being several layers of connective tissue between the two.

The literature is briefly reviewed, and the theories as to the cause of the bony thickening overlying meningeal fibroblastomas are discussed. The hypothesis that the bony thickening is secondary to invasion of the tumor cells is upheld. This case, together with those of Winkelmann, Bucy and Kredel and Cushing, seems to show that the presence of trauma is not a necessary factor in the production of bone or its invasion.

Histologic Observations on the Sensory and Motor Roots of the Glossopharyngeal Nerve and the Vagus-Spinal Accessory Complex. Dr. I. M. Tarlov, Brooklyn.

Previous study of the histologic structure of nerve roots (Tarlov, I. M.: Structure of the Nerve Root: Observations on Identification of Function in Roots of Mixed Cranial Nerves, Arch. Neurol. & Psychiat. **37**:1338 [June] 1937) had provided criteria for the differentiation of sensory and motor roots. On the basis of these criteria it was possible to demonstrate that the glossopharyngeal nerve and the vagus-spinal accessory complex contained certain roots which were chiefly sensory and others which were chiefly motor. It was the purpose of this study to follow in serial section the nerve fibers of these roots to their respective nuclei in the medulla oblongata and thus to test these conclusions.

It was found that the main component of the glossopharyngeal nerve terminates in the nucleus of the tractus solitarius and is therefore sensory. In addition, there is a motor component which arises from the region of the dorsal nucleus of the vagus nerve and probably the nucleus ambiguus and which is represented by the smaller ventramedial root.

The main cephalic portion of the vagus-spinal accessory complex presents nerve fibers which terminate in the nucleus of the tractus solitarius and is therefore sensory. The main caudal portion of the vagus-spinal accessory complex, as well as a small ventromedial portion of the cephalic roots, arises from the dorsal nucleus of the vagus nerve and the nucleus ambiguus. These are therefore motor roots. There is no clearcut demarcation between the cephalic, chiefly sensory, roots and the caudal, chiefly motor, roots.

It was possible, then, to corroborate the following conclusions, which were made on the basis of previous study of the glial structure of nerve roots.

1. The glossopharyngeal nerve presents a large sensory root and a small ventromedial motor root, usually distinct at its origin from the medulla.

2. The vagus-spinal accessory complex presents a main cephalic portion, chiefly sensory, and a caudal portion, chiefly motor; likewise, the delicate roots which occur ventromedial to the large cephalic roots are motor.

DISCUSSION

Dr. Walter Freeman, Washington, D. C.: Dr. Tarlov has shown in an interesting way the division between the motor and the sensory filaments of the glossopharyngeal nerve and the vagus-spinal accessory complex and has drawn attention to the possible functions of the various components. I should like to ask whether in his studies he has observed anything suggestive of the gustatory nucleus in connection with the glossopharyngeal nerve. It seems fairly well established at present that the tractus solitarius mediates general visceral sensibility, the prime evidence being from comparative anatomy, which shows that the tract and its nucleus are well developed in birds, which are known to have practically no taste buds. On the other hand, the cyprinoid fishes have extensive taste buds not only about the mouth and gills but also over the external surface of the body. In these fishes the nuclei mediating gustatory sense are extremely large, with well developed secondary and tertiary tracts. In work that I did a number of years ago on the human fetus, I found among the entering rootlets of the glossopharyngeal nerve an oval nucleus ventrolateral to the nucleus of the tractus solitarius and quite distinct histologically which in my opinion represented the gustatory nucleus. Examination of serial sections in the adult has

disclosed suggestive evidence of a similar nucleus, but one by no means as distinct. There is also in the fetus in connection with the entering rootlets of the facial nerve a nucleus of somewhat similar character, but it is small and by no means so well defined.

DR. I. M. TARLOV, Brooklyn: I have no evidence for a separate gustatory nucleus in connection with the glossopharyngeal nerve. So far as I have been able to determine, all sensory fibers of the glossopharyngeal nerve in man enter the tractus solitarius and its nucleus.

Experimental Retinoblastoma. DR. ARTHUR WEIL, Chicago.

In preliminary experiments dibenzanthracene in melted lard was injected into the corpus vitreum of the rat eye. It soon became evident, however, that in the control rats lard alone produced intense proliferation of different tissues, corroborating the work on the carcinogenic action of lard, olive oil and other fatty mediums in other organs, as reported by Burrows, Hieger and Kennaway (*J. Path. & Bact.* **43**:419, 1936). Between the retina and the lens there developed a dense granulation tissue containing giant multinuclear cells, rich in cytoplasm, which surrounded acicular spaces. Three months after the injection of superheated lard the cytoarchitecture of the retina was still preserved. There was, however, a considerable increase in the size of the retina as a whole, of the inner reticular layer and of the number of cellular elements. The size of the nuclei of the inner nuclear layer had increased from the normal 5 or 6 microns to 8 or 9 microns. Rosettes were found, surrounded by the small cells of the outer nuclear layer. The latter had proliferated during the fifth month, and at this time numerous mitotic figures appeared. The newly formed tiny cells were seen migrating into the inner nuclear layer, and the separation between the two nuclear layers began to disappear. About the sixth month after the injection there began a migration of cells into the inner reticular layer and the optic nerve. Finally, the whole retina was transformed into a dense cellular structure, which filled out the original corpus vitreum and replaced the shrunken granulation tissue. At about the fourth month after the injection of lard the ciliary body showed marked hypertrophy; both papillae as a whole, as well as the covering epithelium, were enlarged.

During the early stages of these experiments of five months' duration some doubt might have existed as to whether one was not dealing with a hyperplastic rather than a neoplastic process or with a granulomatous or a traumatic reaction. However, after six or more months there is no doubt that the proliferation of newly formed retinal cells throughout the corpus vitreum, the invasion of the optic nerve, the replacement of the reticular layers by cellular elements and the appearance of mitotic figures indicate true neoplasia. The term "retinoblastoma" instead of "neuroblastoma" of the retina is preferred, in adherence to Verhoeff's terminology of the human retinoblastoma.

DISCUSSION

DR. F. WERTHAM, New York: I should like to ask whether any definite changes were observed in the ganglion cells of the retina in these cases.

In 1910, Professor Schreiber, of Heidelberg, carried out experiments of a similar nature. He injected scarlet oil into the anterior chamber of the eye in rabbits. He found mitoses and definite hypertrophy in ganglion cells of the ganglion cell layer of the retina and in the outer granular layer (where there are usually no ganglion cells). Professor Schreiber's paper (*Arch. f. Ophth.* **74**:1, 1910) is illustrated only by drawings. I made inquiries about these unique claims from authorities on the pathology of the eye and learned that almost universally Professor Schreiber's observations had been discounted by ophthalmologists. On account of my interest in the pathology of ganglion cell changes in general, I got in touch with Professor Schreiber, and he allowed me to study his original material. I found that the preparations indubitably contained gan-

glion cells which showed either definite hypertrophy or actual mitoses as a result of the experiments. No glia cells, which could be mistaken for ganglion cells, occur in these layers.

I included in our book "The Brain as an Organ" (New York, The Macmillan Company, 1934) two photographs (plates 140 and 141) made from Professor Schreiber's material.

I have wondered why these important observations have not been duplicated.

DR. ARTHUR WEIL, Chicago: Dr. Wertham will find a reference to Schreiber's and Wengler's attempts to produce tumors of the eye and the probable reasons for their failure in a paper which I published, together with Dr. L. L. Mayer (Experimental Retinoblastoma, *Arch. Ophth.* **23**:591 [March] 1940). It now appears likely that their claim that they had observed mitotic figures in retinal cells was justified, though they did not succeed in producing actual tumors of the retina. Mitotic figures may be observed first at about the end of the fifth month.

Lymphogranulomatosis (Hodgkins' Disease) of the Nervous System. DR. N. W. WINKELMAN and DR. M. T. MOORE, Philadelphia.

This paper appears in full in this issue, page 304.

Equine Encephalomyelitis. DR. ALEXANDRA ADLER, Boston.

At Dr. Putnam's suggestion, all the cases (100) in which the diagnosis of encephalitis or encephalomyelitis had been made at the Boston City Hospital since 1928 were reexamined clinically and, when autopsies had been obtained, histologically. Autopsies were obtained in 19 of the 37 cases of fatal termination. In 1 of these the histologic picture can hardly be differentiated from that of equine encephalomyelitis, an epidemic of which occurred in man in Massachusetts in the summer of 1938.

The patient, a 23 year old man, died in April 1936 after an illness of twenty-one days. He had come to the hospital with complaints of chills and pains, which had started eleven days before. Bronchopneumonia was suspected. After two days the patient complained of severe headaches. There were stiff neck, hemiparesis, bilateral ankle clonus and the Babinski sign. The protein content of the spinal fluid was increased to 156 mg. per hundred cubic centimeters, and the number of cells was 1,870 per cubic millimeter, 93 per cent of which were polymorphonuclear leukocytes. The patient died nine days after the onset of neurologic signs.

At autopsy, bronchopneumonia at the base of the lungs was found. There were extensive changes in the central nervous system. As in equine encephalomyelitis, the vessels were cuffed with cells, about half of which were polymornuclear leukocytes. The inflammatory cells were in some places within the wall of the vessel; in others they were confined to the perivascular lymph spaces, and in still other regions they invaded the brain tissue. In addition to the polymorphonuclear leukocytes, there were several macrophages, lymphocytes, plasma cells and gitter cells around the vessels. Myelin stains disclosed areas of perivascular demyelination, which had been reported also in cases of equine encephalomyelitis. No definite changes could be found in the spinal cord. The negative observation would be unusual in cases of postinfectious encephalomyelitis if extensive perivascular demyelinations were in the present cerebrum. The white matter was more involved than the gray matter, whereas the cerebellum was less involved than the cerebrum. No attempt to isolate the virus was made in this case. The reported histologic and serologic findings are suggestive of a sporadic case of equine encephalomyelitis rather than of one of postinfectious encephalitis.

DISCUSSION

DR. ARTHUR WEIL, Chicago: Through Dr. K. F. Meyer, I was able to study 2 cases of the 1937 epidemic of encephalitis (equine?) occurring in man in

Madera and Fresno counties, Calif. The inflammatory reaction consisted of perivascular lymphocytic and plasma cell infiltration and foci of proliferated glia. However, unlike the histopathologic picture in the epidemic encephalitis of St. Louis, the white matter of the cortex was more affected than the gray matter or the nuclei of the midbrain. Furthermore, the glial proliferation tended to spread out diffusely and was not sharply defined in smaller foci.

Fuchsin Stain for Cerebral Blood Vessels. DR. G. EROS, New York.

There can be no doubt that the Pickworth benzidine method of demonstrating blood vessels is a useful procedure for neuropathologic studies. This method, however, can be applied only to fresh material which has been fixed in solution of formaldehyde U. S. P. for a few days. In brains fixed in solution of formaldehyde for months the results are poor. Moreover, the Pickworth preparations often fade rapidly and cannot be studied after a few weeks. These reasons prompted me to devise a method of demonstrating the network of cerebral blood vessels which (1) could be applied to old material and (2) would give permanent preparations.

Acid fuchsin is used in this method to stain erythrocytes. In order to demonstrate the network of vessels, as in the Pickworth method, thick sections are necessary. These thick sections take up the dye to such an extent that it is difficult to differentiate the stain, and consequently there is no clear contrast. On the other hand, if one stains thinner sections the result will not be satisfactory, since the network of vessels will not be demonstrated as clearly as in thick sections. Mandelstamm has devised a method for demonstrating blood vessels by employing a concentrated solution of acid fuchsin and combining it with Mallory's procedure. He used, however, relatively thin sections; the network of vessels therefore cannot be visualized. Particularly, smaller areas lacking blood vessels may thus escape attention.

The present method overcomes this difficulty. The method is suitable for staining frozen and paraffin as well as pyroxylin sections. The sections are 120 to 150 microns thick. In the case of paraffin and pyroxylin sections the embedding materials have to be dissolved with xylene and acetone, respectively, before staining. The essence of the method is as follows: After preliminary acidification, the sections are stained in a very dilute solution of acid fuchsin and differentiated with a mixture of 0.5 per cent solution of phenol and lithium carbonate. After differentiation, they are again acidified in hydrochloric acid. The network of vessels is thus demonstrated sharply and makes a striking contrast to the areas devoid of blood vessels.

The details of the procedure are as follows: The sections are acidified in a diluted solution of hydrochloric acid, 3 to 4 drops of concentrated hydrochloric acid being added to 150 cc. of distilled water for several hours, and then washed in distilled water. They are stained in a very dilute aqueous solution of acid fuchsin, made by adding 5 to 6 drops of 1 per cent solution of acid fuchsin to 150 cc. of distilled water. After twelve to fifteen hours, the sections are washed in distilled water and placed in a 1 per cent solution of phenol for one to two minutes, then differentiated in a 1 per cent solution of phenol to which a few drops of 1 per cent lithium carbonate are added. The differentiation must be continued until the ground substance is decolorized and the network of vessels becomes apparent. Overdifferentiation should be carefully avoided. The sections are then transferred into a diluted aqueous solution of hydrochloric acid for ten minutes, washed in water, dehydrated in alcohol, cleared in 10 per cent carbolxylene and xylene and mounted in balsam. Sometimes when the slides are not acidified enough they fade.

Better results are obtained with paraffin and pyroxylin sections than with frozen sections. Both paraffin and pyroxylin sections are mounted on the slide only after staining. If the paraffin block is too fragile to be cut at 120 microns, the paraffin is dissolved with xylene and frozen sections are cut after hydration of the block.

As a preliminary orientation, a fairly good picture of blood vessels can be obtained in frozen sections stained with diluted fuchsin for twelve hours without previous acidification and without differentiation.

The method is not as sensitive as that of Pickworth, but it has the following advantages: 1. It can be applied to old material. 2. Sections can be preserved for a relatively long time. 3. There are no precipitations around the vessels, such as are easily found in the Pickworth preparation. The picture, therefore, is clearer. 4. The method is excellent for demonstrating hemorrhages. 5. The Nissl stain can be applied to sections from the same block.

This method cannot be applied to poorly fixed material because of decay of erythrocytes in consequence of insufficient fixation. The importance of good fixation should be stressed. If, for instance, the brain is fixed *in toto* and the solution of formaldehyde fails to penetrate into the deepest portion of the sulci, the erythrocytes in this region fail to be stained. Well fixed material, therefore, is necessary. When well fixed material is available, the stain gives good results, even after years of fixation.

Changes in Vascular Pattern Following Experimental Trauma of the Brain. Dr. M. Helfand, New York.

Utilizing the Lepehne and Pickworth benzidine stain, an experiment was undertaken to ascertain in animals the occurrence of vasomotor changes in the brain following trauma of the skull. For control purposes, an average normal vascular pattern of various areas of the brain was obtained by the study of the vascular pattern in 5 normal cats. In addition, 11 cats were exposed to trauma varying in intensity and number of injuries, with different intervals of life between the trauma and killing of the animal.

The pathologic studies of the brain material revealed many more or less localized disturbances in the regularity of the vascular pattern. These changes varied from complete lack of staining of the intravascular contents and distortion in the regularity of the caliber of the blood vessels to dilatation and engorgement of the vessels. The latter was at times accompanied by diapedesis.

The Nissl stain revealed many areas of ischemic cell changes either circumscribed or diffusely spread in the upper layers of the cortex. They did not always correspond to the disturbance in the vascular pattern as revealed with the benzidine stain.

The disturbances of the vascular pattern represent pathologic states of vascular performance. These physiologic dysfunctions of the blood vessels may be reversible, depending on the intensity and duration of the trauma. When the circulatory dysfunction is lasting, the ganglion cells disclose structural changes, varying from ischemic alteration of individual cells to more or less circumscribed areas of necrosis.

PHILADELPHIA PSYCHIATRIC SOCIETY

Lauren H. Smith, M.D., *President, in the Chair*

Regular Meeting, Oct. 11, 1940

A Paranoid Reaction with Manifest Homosexuality. Dr. Donald W. Hastings.

In 1911 Freud (Psychoanalytic Observations Concerning an Autobiographically Described Case of Paranoia, *Jahrb. f. psycho-analyt. u. psychopath. Forsch.* **3**:9-68, 1911) described the paranoid reaction as it seemed to be related to homosexuality. As a result of this study, he advanced the theory that repressed

homosexuality may be projected to give the paranoid syndrome. This relationship has subsequently been noted by a number of observers. The situation described in the following case report is interesting in that the homosexuality was overt and clearly recognized by the patient.

A white woman aged 49, a domestic, applied at the clinic for psychiatric help on Aug. 4, 1937—"to find out if I am insane or whether every one I come in contact with is plotting against me." The patient was one of a group of servants. Shortly after her arrival in the household (on May 28, 1937) she began to feel that the other female employees were talking about her and making fun of and ridiculing her. After two weeks of employment in this household, the patient quit her job because she felt under constant criticism and ridicule. So far as is known, she had no hallucinatory episodes at any time during the illness.

This set of symptoms continued from April through August 1937. During this time the paranoid picture remained constant. There was poor insight into the fact that the symptoms were delusions. When the patient was seen on Sept. 28, 1937, the overt paranoid picture had disappeared and she regarded herself as "very silly in imagining all these things."

She had never had any interest in the opposite sex, and felt that there was something repulsive about men. She did not, however, regard herself as homosexual until the age of 24, when she began to room with another girl of the same age. Overt homosexual relations were established and were continued with the same partner for twenty-five years, until the time of her illness. In this relationship the patient was the aggressive member. In the early spring of 1937 the partner became attracted to a younger woman and left Philadelphia to live with her. This was a great blow to the patient, and in the attempt at adjustment there developed the paranoid delusions already described. At this time the patient received a letter from her former partner, saying that she was not satisfied and asking if she could came back to live with the patient. This was coincidental with the disappearance of the paranoid delusional system. A month later the patient was happily employed as the chief of maids in a household and was corresponding frequently with her former partner. Plans were under way for the resumption of their living together.

On apparent recovery the patient had poor insight into any connection between homosexuality and her set of symptoms. She clearly recognized that she was homosexual, but felt that her symptoms were due to the fact that she was "upset over being jilted by a friend of twenty-five years."

The results of physical and neurologic examinations were within normal limits. In appearance, the patient tried to deny her sex by having a man's haircut and wearing suits with a marked masculine cut and men's oxford shoes. She was brusque and business-like.

Two years later (Aug. 13, 1939) the patient was interviewed. The following is a brief résumé of her story: When she last visited the clinic, in 1937, her friend and she were planning to resume living together. This plan, however, had not yet been accomplished, but the two had been corresponding frequently.

The patient stated that she had had a recurrence of the feeling that the employees in the former household were ridiculing her. "They had it in for me, and I am sure that I am right." There were no other delusions or ideas of reference which could be elicited. The patient still regarded herself as being completely well mentally and had good insight into the fact that she had been "very ill" during the time she was attending the clinic in 1937.

Comment.—The work of Freud and others seems to indicate that if homosexuality is repressed it may reappear in paranoid delusions and the schizophrenic syndrome. In this particular case the homosexuality was not repressed, but was simply blocked in its overt expression. During a period of twenty-five years in which it had been allowed free expression no symptoms had developed.

Thus, on the basis of the present case, it might be postulated that when the expression of homosexuality is blocked consciously from its goal, the same type

of paranoid delusion may be formed as when it is repressed. In this case the delusions were not as severe as those seen in typical paranoid schizophrenia, nor were hallucinations present. It could be theorized that the conscious blocking of this sexual impulse produces less intense symptoms than its repression.

DISCUSSION

DR. LAUREN H. SMITH: All are familiar with the theory of the relation of paranoid syndrome to homosexuality, both in freudian and in other concepts. This, of course, is based on the idea of repression. In the present case the syndrome was clinically manifest as an overt and understood situation, the repression not being particularly apparent.

Asymptomatic Vertebral Fractures in Cases of Epilepsy: Comparison with Vertebral Fractures Due to Metrazol-Induced Convulsions. DR. MATTHEW T. MOORE, DR. N. W. WINKELMAN and DR. LEON SOLIS-COHEN (by invitation).

Recently there have appeared in the literature several articles calling attention to compression fractures of the vertebrae resulting from therapeutic metrazol-induced convulsions. The implication may be to regard this as a serious indictment of this type of therapy and, indeed, to interdict the use of metrazol even in those psychiatric conditions which respond most favorably to its use. The problem at hand is to determine whether a treatment which has yielded favorable results in such conditions as involutional psychoses and depressions should be summarily dismissed because of a complication which in itself may not be of great moment.

The metrazol-induced convulsion is similar in many respects to the severe convulsive seizures seen in the grand mal type of epilepsy. If the muscular activity in the grand mal fit is of equal intensity and produces the same mechanical action on the vertebral column as that in the metrazol-induced convulsion, then vertebral fractures also should be encountered here.

In order to determine the frequency and seriousness of the complication of vertebral fractures, both immediate and remote, we selected at random a small group of 12 "epileptic" patients who had had severe grand mal seizures and made roentgenographic studies of their vertebral columns. We endeavored to elicit a history of pain in the back and possible orthopedic and neurologic disturbances which might be due to injury to the spine.

These 12 patients all at some time had had severe grand mal seizures; the duration of the illness ranged from two to forty-four years, with an average of sixteen and one-half years. It will be seen from the roentgenographic studies of the vertebral column in these cases that 11, or approximately 92 per cent, of the patients sustained some sort of injury to the spine. Assuming that the lesions presented by patients 1, 4 and 5 might be considered as borderline, or perhaps questionable, there still remain 66.6 per cent in whom definite fractures or injury of the vertebrae occurred.

As more patients subjected to metrazol shock treatment come under careful roentgenographic study, there is no doubt that additional instances of vertebral fracture will be reported in the literature.

Many of the complications, we anticipate, will be avoided or satisfactorily resolved by increased experience and a better understanding of the factors producing them. Several methods have already been suggested to prevent the occurrence of vertebral fractures. We have been using a procedure which has to recommend it, first, simplicity of application and, second, apparent effectiveness. Briefly, this method consists of using a bed equipped with a hard, even mattress with boards placed between it and the springs, thus making in effect a rigid orthopedic bed. The patient is placed on his back; an attendant on each side holds the arm and shoulder down and firmly against the body (preventing fracture or dislocation of the humerus or shoulder joint); another attendant fixes the pelvis and legs firmly against the mattress, and a fourth attendant cups the left hand under the jaw and chin and with the right hand holds padded tongue depressors between

the teeth, a presentation which tends to avoid fracture or dislocation of the jaw and biting of the tongue. By this method the patient is fixed firmly against a flat, unyielding surface and the vertebral column is maintained in a position which prevents acute flexion.

The ultimate effects of vertebral fractures caused by metrazol-induced convulsions cannot as yet be determined. If one may use as a criterion the results of study in the small group of cases reported here, in which fractures of the vertebral column were demonstrated in epileptic patients who despite their injuries offered no complaints referable to them and showed no orthopedic or neurologic sequelae, then it bids fair to expect no orthopedic or neurologic disturbances of great moment or in great number following vertebral injuries due to metrazol shock therapy. The efficacy of metrazol convulsive therapy versus conservative methods in management of the psychoses must in the long run be the determining factor which tips the scales against the uninvited complications of vertebral fractures and other accidents.

This paper will be published in full in the *Journal of Nervous and Mental Diseases.*

DISCUSSION

DR. LAUREN H. SMITH: I should like to ask Dr. Moore whether any previous observers have made such a study on a large scale.

DR. JOSEPH HUGHES: Has Dr. Moore found that he can prevent vertebral fractures in metrazol-induced convulsions by means of suitable restraint? Is the incidence of fracture in the series of cases in which electric shock was employed at the Philadelphia General Hospital less than that in cases in which metrazol is used?

DR. WILLIAM FURST, Norristown, Pa.: About six months ago I presented a similar paper before the Philadelphia Neurological Society (The Force Required in Crush Vertebrae: Its Probable Mechanical Relation to the Post-Metrazol Fracture, *Psychiat. Quart.* **14**:397, 1940); ARCH. NEUROL. & PSYCHIAT. **44**: 687 [Sept.] 1940), stressing that the flexion force placed on a vertebra during the metrazol convulsion probably ranges between 250 and 750 pounds (125 to 375 Kg.). In order to prevent this compression effect it seemed to me necessary to emphasize the importance of counterpressure. In a series of 37 patients treated with metrazol at the Norristown State Hospital, the incidence of vertebral fractures was 8 per cent. I attributed this low figure to the emphasis on maintaining hyperextension of the vertebral column. In reply to Dr. Hughes's question, I should like to report the occurrence of 2 vertebral fractures in a series of 40 patients undergoing electric convulsive treatments at the Philadelphia General Hospital.

DR. MATTHEW T. MOORE: In answer to the question regarding studies among large groups of epileptic persons: Reed and Dancey (*Canad. M. A. J.* **42**:38, 1940) made roentgenographic studies of the vertebral columns of 72 patients with idiopathic epilepsy and of 86 patients subjected to metrazol and insulin shock treatment. Of the 72 patients with epilepsy, they found 34.2 per cent with compression fractures of the vertebrae, which were asymptomatic and without orthopedic complications. Of the patients having convulsions induced by shock therapy, vertebral fractures were found in 31.4 per cent.

Since we have been employing the method described, we have been extremely fortunate in having had no fractures. The convulsions produced by the electric shock method are not as severe as those induced by metrazol, but despite this, fractures have already been reported to follow its use. It is evident that in the application of electric shock therapy, even though the element of fear has been eliminated, the possibility of trauma must still be overcome.

Stephen Collins Foster. DR. JAMES H. WALL, White Plains, N. Y. (by invitation).

More recent students of alcoholism have observed the frequency with which a deep mother attachment is met with in male patients. The life of Stephen Collins Foster is an illustration of this observation.

The spirit of the antebellum South, revived so romantically in recent best sellers, has been captured even more vividly in the melodies of Stephen Collins Foster. Foster, however, spent only a few days of his life below the Mason and Dixon Line, and it is of interest to the physician to read the meager records of his hospitalization at Bellevue, where he died in January 1864.

As his songs and his life show such a deep love of home and parents, his family background is an important consideration. He was the ninth of 10 children. His father was not a successful man and had no sympathy with Stephen's musical ambitions. From his mother, to whom he was devoted, he inherited his poetic and musical temperament. The family life appears to have been extremely happy and the mother and older children seem to have lavished affection on Stephen, who was born in Pittsburgh on July 4, 1826.

He was a frail, but attractive, child who early showed his talent and who was most unhappy when separated from his mother in school. This inability to adjust to any group away from home persisted. At the age of 15 he left boarding school, to remain with his mother until he was 20. Much of his time was devoted to writing and playing music, although he had little intensive training. Finally his family, disappointed in his lack of interest in business, sent him to Cincinnati as a bookkeeper. There he began to compose the songs for which he is famous, "O, Susanna" being the first of these.

After four years he moved back to Pittsburgh and married, in 1850, Miss Jane McDowell, "Jeanie of the Light Brown Hair," whom he took home to live with his parents. The marriage proved an unhappy one, and Stephen's disposition became morose and introspective. He began to turn to alcohol. His songs also underwent a change and took on a quality of yearning for the happiness of bygone days. "My Old Kentucky Home," "Old Folks at Home" and "Massa's in the Cold, Cold Ground" belong to this period.

In 1855, when Stephen was 29, his father and mother died and he started to drink heavily and to drift financially. His wife left him and became a telegraph operator to support her child. Finally, at the age of 34, Stephen came to New York alone, where he spent much of his time with drinking companions and did little work. After three or four years, during which time his friends said that he ate little, wept easily and always appeared anxious and startled, he was found one winter morning in a bowery lodging house with his throat cut and his forehead bruised. He was taken to Bellevue Hospital, where he died alone a few days later.

In his songs Stephen Foster wrote about the South in a way that no native southerner could have done. The art of Foster's music lies somewhere between the desire for a thing and its complete realization. Foster's own longing for home and his strong attachment to his mother make up the predominant theme of his songs. The association of warmth, comfort, ease, laziness and dependence suggested by the old South have a definite relationship to a mother's love. The melodies of Stephen Foster stir in most persons the same feeling of infantile love of mother and home, the driving force of Foster's life.

Application of the Rorschach Test to Practice in Mental Disease Hospitals. DR. JOHN C. URBAITIS and DR. JOHN WATERMAN (by invitation).

The Rorschach test was administered to 125 patients in two closed mental disease hospitals. The patients were easily available to the examiner so that the test was administered when a reasonable amount of cooperation could be obtained. At least 30 responses were given by 25 per cent of the patients, and only a few gave no scorable responses. To the patients who gave few or no scor-

able responses the cards seemed to act as a nondirectional stimulus. The material presented approached that which might have been obtained by free association. In the case of patients who had ideas of reference the responses to the Rorschach test reflected this trend. Occasionally material which could no longer be elicited in formal psychiatric interviews was demonstrated in the responses to the Rorschach test. The test indicated the presence of residual schizophrenic trends in patients who otherwise showed marked improvement or apparent recovery.

When used as a technic in the complete study of patients in a mental disease hospital, the Rorschach test (1) often confirms diagnostic impressions, (2) elicits material not always obtainable by other methods and (3) helps in formulating the prognosis by indicating the presence of psychopathologic trends.

DISCUSSION

DR. KENNETH APPEL: Has there been any application of this test to neurotic children? While I was working with encephalitic children at the Pennsylvania Hospital I stumbled on what were called "blottos." I saw them in the newspaper and made a series for work with these children; I found that they were helpful in getting some of the patients to speak about their fantasies. Occasionally I have used this method to gain the cooperation of children. This indirect method of approach does away with the formal examination, gets them to talk about things which ordinarily they would not mention and generally is helpful.

DR. ROBERT A. MATTHEWS: I should like to ask the authors whether in any particular case it became necessary to make a definite revision of the clinical diagnosis after a Rorschach test.

Also, have the authors had any experience in the use of the Rorschach test with those patients who offer the difficult diagnostic problem which, for the lack of a better name, is sometimes called schizomania—those patients whose past personality has not been definitely schizoid but whose illness shows a combination of manic and schizoid characteristics?

DR. PHILIP Q. ROCHE: I wish to ask Dr. Urbaitis if he can say what position the Rorschach experiment holds in relation to a number of the so-called personality tests more commonly employed, for example, the Woodworth inventory scale. I should like also to know whether the authors have an opinion as to the comparative usefulness of the Rorschach test and the Woodworth inventory scale and similar technics in making estimates of personality and in utilizing such data for prognosis.

DR. JOHN WATERMAN: I can say only that in our experience with 125 tests, which is not a great many, we do feel that the Rorschach test is of definite value and that we obtain information we might not obtain with other methods of examination.

In reply to Dr. Roche's question about the value of the Rorschach test as compared with that of the Woodworth inventory scale and similar tests, which are more easily administered than the Rorschach test: I think that the latter has a distinct advantage over the other so-called personality tests in that it involves no right or wrong answers. The patient is asked, "What do you see?" Regardless of what he replies, or even if he refuses to answer or there is no scorable response, one still has something which will serve to act as an indicator of his personality. In some of the other tests one has no way of interpreting certain responses. When questions are asked which may be answered with "yes" or "no," the patient may give the answer which he thinks is the right one, but which actually does not represent his true feeling in the matter. With the Rorschach test this sort of thing makes little difference, for if the patient invents something or points out something which cannot be clearly seen, one has a means of scoring it and thus obtains a clue which will assist in getting a picture of the personality makeup of the patient.

With regard to the question whether it has been necessary to revise the clinical diagnosis on the basis of the findings in the Rorschach test, I cannot cite any particular case in which we have had to revise the clinical diagnosis. When

we have seen schizoid trends in an otherwise obviously manic patient and it has been difficult to determine whether the diagnosis should be schizophrenia or mania, our findings in the Rorschach test have sometimes shown a preponderance of underlying schizophrenic trends. Later, some such patients have shown full-blown schizophrenia. I shall not attempt to discuss all of the criteria in the Rorschach responses which are considered indicative of a schizophrenic trend. I may give one example, however: When a patient has strong schizoid tendencies, he will pay undue attention to rare and insignificant details in the Rorschach ink blot. In Beck's most recent monograph (Personality Structure in Schizophrenia: A Rorschach Investigation in 81 Patients and 64 Controls, Nervous and Mental Disease Monograph 63, New York, Nervous and Mental Disease Publishing Company, 1938), he contends that this character of response is more or less characteristic of schizophrenia. As I said, there are other criteria which are indicative of schizoid tendencies, and when these appear in cases of clinically diagnosed manic-depressive psychosis, one has a clearer picture of the patient's future course.

With respect to Dr. Appel's question, I cannot cite them accurately, but there have been publications with regard to the use of the Rorschach test with inhibited, feebleminded and neurotic children. There is a good bibliography in Beck's monograph on work with children. Studies have been made on groups of children, not very large groups but I think with a fairly wide age range. I know of one group of children from 10 to 14 years.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

BRONSON CROTHERS, M.D., *President, in the Chair*

Regular Meeting, Oct. 17, 1940

Relation of the Cortex to the Basal Ganglia in Integration of Motor Activity in the Infant. (Lantern slides.) DR. MARGARET A. KENNARD, New Haven, Conn.

It seems to be a fact that when a lesion of a given area occurs in the cerebral cortex of a human infant the resultant motor deficit is far less than that which appears when the same area is injured in an adult. Consequently, the so-called cerebral palsies which result from changes in the brain before and during birth are usually the effect of widespread injury to cortical tissue, and lesions such as porencephalies may be relatively large, but still symptomless.

Another fact well brought out by the clinical histories of infants which were studied in the Children's Hospital, Boston, is that the motor deficit from lesions present at birth may not appear for many months thereafter.

Experiments on young monkeys and chimpanzees have shown that there is the same difference between the young and the adult in these species of primates also; some of the results of such experiments will be shown in the accompanying moving picture.

In this film it is shown that in the adult unilateral removal of the motor areas corresponding to Brodmann's areas 4 and 6 produces moderate hemiparesis and that bilateral ablation of these areas results in abolition of all voluntary movement. Reflex grasping and the other simple reflex movements which remain are demonstrated. Next is shown an infant baboon after bilateral ablation of the same areas. This animal can walk, climb and feed itself adequately. Unilateral removal of these areas at this age is shown to be followed by almost no change in motor performance.

In seeking for the reason that motor function remains "voluntary" and skilled movements are possible in the infant after removal of all cortical motor areas, two possibilities present themselves: Either the remaining cortical areas which are not concerned with motor performance in the adult are able in the infant to

integrate such complex coordinate movement after the true motor areas have been removed, or else at this age, at which the cortical tracts are known to contain little myelin, the subcortical centers perform a great function. Ablation experiments show that both the cortex and the subcortex play a part in integrating motor activity but that the caudate nucleus is relatively much more important than the cortex for the normal performance of the infant.

Both these possibilities receive support from evidence in the film: the first, that the "nonmotor" areas of the cortex affect motor performance even at 3 weeks of age, by the fact that an infant with ablation only of areas 4 and 6 on the left side shows practically no difference in posture or movements between the extremities of the two sides, whereas an infant with one hemisphere absent shows a definite, although slight, impairment of contralarteal motor function.

All the ablations from cortical areas which have now been made on a series of about 40 infants have demonstrated this slight but definite effect of cortex on motor function in the infant. In addition, they have shown that such deficit, although slight immediately after operation, becomes much more pronounced as the animal grows, particularly during the second six months of life, when spasticity becomes more pronounced.

In contrast, when the caudate nucleus is removed in addition to area 6, or to areas 4 and 6, immediate and apparently permanent severe alterations appear. The last 2 monkeys shown in the film are infant macaques, each operated on at the age of 3 weeks. One, with bilateral extirpation of area 6 only, is able to run, to climb and to grasp my hand or the bottle in a normal manner. The other has also had bilateral ablation of area 6 and, in addition, removal of all the caudate nucleus underlying this region on either side. It will be seen that the animal is unable to use its hands for grasping or climbing and that motor progression even now, at the age of 6 months, is limited. Furthermore, the posture of the hands is strikingly like that seen in the "pill rolling" posture of a patient, and the movements are often sufficiently irregular and poorly coordinated to resemble athetosis.

Combined lesions of area 6 and the caudate nucleus have been made on a series of adult monkeys also. The syndrome of reflex grasping and spasticity produced by bilateral ablation is altered by the addition of a fine tremor when the caudate nucleus is removed as well. In the older animals, however, cortical ablation is followed by relatively profound deficit and lesion of the caudate nucleus by comparatively little.

DISCUSSION

DR. LEO ALEXANDER: This is an excellent paper, and I am much impressed by the results of the study. It is the first time that this work has been done in higher animals, and it indicates that the basal ganglia as well as the cortex are extremely important in the control of movements. I wonder whether there have been observed any more definite athetoid movements than those shown in the pictures. From the moving pictures I could not be sure whether the movements were athetoid.

DR. STANLEY COBB: The disability in these animals reminds me somewhat of that which Dr. Mella produced in our laboratory about fourteen years ago by giving manganese. Those animals, also, had some movements which were a little shaky, similar to those shown in the moving pictures.

DR. PAUL I. YAKOVLEV, Waverley, Mass.: From clinical experience it appears that there exists a relationship between the level of general intelligence and the degree of potential compensation of motor deficiencies caused by congenital and early acquired cerebral lesions. For example, in the case of a child of 3 or 4 years afflicted with Little's spastic paraplegia and unable to walk the prognosis as to eventual ability to walk is rather favorable provided the child shows no gross mental defect. Such a child may never walk normally, but usually by the age of puberty he learns to walk after a fashion and without assistance. On the other hand, if such a child is an idiot or an imbecile the prognosis as to erect, i. e., bipedal, locomotion is poor. By the age of puberty such a child learns at best to crawl about; usually he remains bedridden. I should like to ask Dr. Kennard whether observations are available as to the relation between the compensation

of motor functions in animals in which the motor and premotor regions have been removed and the integrity or simultaneous involvement of the frontal associative fields, i. e., the parts of the frontal lobes situated anterior to area 6.

DR. JAMES C. WHITE: I should like to ask Dr. Kennard to comment on the plantar response of these animals in relation to the other changes found to depend on the age at which ablation was done.

DR. JAMES B. AYER: I wish to compliment Dr. Kennard on this splendid piece of work and the excellent pictures. Can she make any statement about the relation of stage of development of the nervous system, myelination, and the like, to the effect of localized lesions at various ages?

DR. H. HOUSTON MERRITT: Does involvement of the basal ganglia make any difference in regard to the development of spasticity?

DR. MARGARET KENNARD, New Haven, Conn.: In reply to Dr. Alexander regarding athetoid movements, my associates and I have not seen any more definite athetoid movements than those shown in the pictures. We produced an excellent case of hemichorea in a half-grown chimpanzee which lasted three weeks and disappeared completely, but we have not been able to repeat this.

In regard to the effect of intelligence on motor defects, we have considered that. Dr. Jacobson, in St. Louis, has performed various psychologic tests on infant animals with frontal lesions to see whether they measure up to adults with similar lesions. I do not yet know the results. I think that when all the frontal association areas are removed in infancy the animals do not show any greater recovery of psychologic functions than when similar ablation is done in adult life. As controls we also made ablations of both occipital lobes in infant monkeys. Those infants are totally blind. Dr. Jacobsen still has a number of our animals; I am not sure about the total intelligence of animals with lesions of the frontal lobe.

Dr. White asks about the plantar responses. This reflex is difficult to test in these animals and the Babinski response does not occur in monkeys, but the deep reflexes are increased.

As to the question of spasticity and flaccidity: Infants with cortical ablation show no degree of spasticity until the sixth or eighth month of life, when it develops. I cannot tell about the animals with lesions of the basal ganglia, since their lesions are only a few months old. The 8 month old infant monkey certainly has some degree of spastic rigidity. Its knee and biceps jerks are not much increased, certainly not increased as are those of animals with only cortical ablations. We shall know in a year whether greater spasticity will develop in the animals with basal ganglia and cortical lesions as they grow older.

I cannot answer Dr. Ayer's question. There is little known about the histologic structure of the brain of normal animals of this age. A few studies have been made on animals, and as far as I can find out the pyramidal tract is myelinated, but not completely so, at birth. These studies, which were done long ago and are not of much help, are the only ones that I can find.

Development of the Human Cerebral Cortex During the First Month of Life. DR. J. LEROY CONEL.

Among other objectives, this investigation is concerned with the observation of changes in structure which occur in the human cerebral cortex with advancing age, starting with that of the full term fetus at birth. Study of the cortex of the newborn and of the 1 month old infant has been completed, and the two stages of development may be compared.

There are slight gross differences between the brains at these two ages. According to the figures of Coppoletta and Wolbach (*Am. J. Path.* **9**:55-70, 1933), there is a difference of 78 Gm. in the weights of the entire brain (newborn, 335 Gm.; 1 month old infant, 413 Gm.). The brain of the 1 month old infant is much less gelatinous and is firmer to the touch than that of the newborn.

There is considerable variation in the general shape of brains of the same age; therefore linear measurements are of little significance in respect to increase in size. The brain of the 1 month old infant is probably about 1 cm. longer and

1 cm. higher than that of the newborn. The lips of the operculum are slightly closer together in the 1 month old infant than in the newborn. The gyri appear to be of about the same size at these two ages, but the sulci seem slightly narrower at the age of 1 month.

For the purpose of following growth changes and making comparisons in the microscopic structure of the cortex, the following criteria may be used: (1) width of the entire cortex and of each horizontal layer, (2) number of nerve cells, (3) size of nerve cells, (4) condition of chromophilic substance, (5) presence of neurofibrils in neurons, (6) size and length of processes of nerve cells, (7) presence of pedunculated bulbs, (8) appearance of varicosities, (9) size and quantity of exogenous fibers and (10) state of myelination. A change occurs in each of these criteria with advancing age. The architectonic areas of von Economo (The Cytoarchitectonics of the Human Cerebral Cortex, London, Oxford University Press, 1929) and Koskinas are used.

The width (thickness) of the cortex increases with advance in age. During the first month of postnatal life there has been a slight gain in the total width of the cortex in all areas in the occipital lobe, in three fourths of the areas in the frontal lobe and in two thirds of the areas in the parietal and temporal lobes and no gain in the insula and gyrus cinguli. When the total width of the cortex is analyzed according to the horizontal layers, it is found that a gain in width has occurred more consistently in layer V than in any other layer. There has been no gain in the width of layer V in the region of the lower extremity in gyrus centralis anterior. The greatest gain in the width of layer V is in the region of the trunk, shoulder and arm in gyrus centralis anterior. Layer II has gained the least. In general it can be said that layers IV, V and VI show a gain in width more consistently than layers II and III.

On the whole, there are a slight increase in the size of the nerve cells and a slight decrease in the number of cells to the unit during the first month of postnatal life. The large pyramidal cells in layer V are more consistent in showing an increase in size than any others, and the cells in layer II show the least gain.

Nissl bodies are not present in any cells in the cortex of the newborn. A few definitely formed Nissl bodies are present in the giant pyramidal cells of Betz in the region of the hand. No Nissl bodies are formed in any other cells in the cortex of the 1 month old infant. In respect to differentiation of the chromophilic substance, the auditory receptive area is more advanced in development than either the visual or the somesthetic area.

In the cortex of the newborn neurofibrils are present in all giant pyramidal cells in the region of the trunk, shoulder and arm, in only the largest of these cells in the region of the lower extremity and in a few giant cells in the region of the hand. These structures are not seen in any other cells. In the 1 month old infant neurofibrils are present in the giant pyramidal cells in the same regions as in the newborn and have developed in all the giant cells in the region of the hand.

The dendrites and axons of all nerve cells have increased in caliber and length during the first month of postnatal life. The processes of the giant pyramidal cells in gyrus centralis anterior are the largest and longest, and those of the cells in the region of the hand show the greatest gain in development beyond the condition in the newborn. In all areas of the cortex the processes of the extra large pyramidal cells in layer V show more increase in development than any other cells, and the cells in layers II and III show the least increase.

Structures called spines and thorns are present on the dendrites of nerve cells in the cortex. One variety of these resembles a clover leaf. It consists of a small bulb attached to a dendrite by a slender stalk. A small hillock is present in the dendrite at the point of attachment. These bulbs increase in quantity with advancing age. In the 1 month old infant they are most numerous on the dendrites, particularly the apical dendrites, of the giant pyramidal cells in gyrus centralis anterior. In other areas they are more numerous on the extra large pyramidal cells in layer V (the homologues of the giant pyramidal cells) than on any other cells. There are very few of these bulbs on the dendrites of cells in layers II and III.

The axons of cells of Golgi type II form a mesh of fine fibers in all layers throughout the cortex. This mesh is densest in the receptive areas. The mesh increases in density in all these areas during the first month of postnatal life, but the somesthetic area shows the greatest gain in this respect.

The fibers which invade any area of the cortex from more or less distant centers are called exogenous fibers. They increase in number and size during the first month. In both these respects the exogenous fibers in layers V and VI show a greater increase than those in the other layers. Also, these fibers have increased in number and size to a greater degree in the area of the giant pyramidal cells in the gyrus centralis anterior than in any other part of the cortex.

During the first month of postnatal development there has been only a slight increase in myelination of nerve fibers. In the 1 month old infant, as in the newborn, myelin is greatest in quantity in the region of the trunk, shoulder and arm in gyrus centralis anterior. It has increased in quantity in all parts of the anterior central gyrus, but the gain has been greater in the region of the hand than in either the region of the lower extremity or that of the head. In the frontal lobe myelin decreases rapidly in quantity toward the frontal pole, where there is but a slight trace of it. There is a slight increase in myelin in the gyrus centralis posterior, very little increase in the auditory receptive area and only a slight increase in the visual receptive area.

In general, it may be said that there has been a slight advance in development of the nerve cells in the cortex during the first month of postnatal life. The increase has been rather uniform throughout the entire cortex, with no centers showing any special growth activity. By all criteria the primary motor area in gyrus centralis anterior shows a greater advance in development than in any other part of the cortex, and within this area there has been a marked increase in the region of the hand. In all areas of the cortex there has been greater advance in development of the neurons in layers IV, V and VI than in layers II and III.

DISCUSSION

DR. JAMES B. AYER: This paper correlates well with Dr. Kennard's from the point of view of development of the nervous system.

DR. STANLEY COBB: The Nissl specimens appeared to be rather darkly stained. If the cells have no Nissl bodies, what is taking the stain?

DR. J. LEROY CONEL: In the very young cells the Nissl, or chromophilic, substance is diffused throughout the entire cell. Later it becomes agglutinated around the wall of the cell and the nucleus, and later still flakes begin to form. At first these are small; then they increase in size. Finally the flakes assume a definite pyramidal shape, which is characteristic of Nissl bodies.

DR. MARGARET KENNARD, New Haven, Conn.: Does Dr. Conel have any information about the basal ganglia? Some authors have stated that the basal ganglia are myelinated at birth.

DR. J. LEROY CONEL: I have not made a thorough study of the basal ganglia in my studies of the cortex, but I have observed the basal ganglia and do not believe I should agree. There is little myelin in the basal ganglia at birth. The small amount of myelin in this region is principally confined to the internal capsule, and that is not very dark. In the 1 month old infant it is a little darker, but not much. With the microscope one can see fibers emerging from the basal ganglia in the newborn.

Evolution of Hemiplegias in Infants. DR. RANDOLPH K. BYERS.

Experience in a physical therapeutic clinic has shown that a number of babies thought to have brachial palsy during early infancy were in reality suffering from cerebral palsies which involved the arm and leg and which months or years later were found to be hemiplegic in most instances.

Papers by McNutt, by Langworthy and particularly by Kennard have suggested an explanation of this mistake. In brief, Langworthy (Relation of Onset of

Decerebrate Rigidity to the Time of Myelinization of Tracts in the Brain Stem and Spinal Cord, *Contribut. Embryol.* [no. 89] **17**:125, 1926; Development of Behavior Patterns and Myelinization of the Nervous System of the Human Fetus and Infant, *ibid.* **24**:3, 1933) showed that decerebration of newborn animals whose period of gestation was short and whose young were immature produced a different physiologic preparation than decerebration carried out on newborn infants of species with relatively long periods of gestation and relative competence in their newborn.

McNutt (Apoplexia Neonatorum, *Am. J. Obst.* **18**:73-81, 1885) reported autopsies on 2 children who died on the sixth and the twenty-first day of life, respectively, and who during life showed first paresis of an arm and later signs of increasing intracranial pressure. Both infants had massive hemorrhages overlying the opposite cerebral cortex and compressing it, especially in the region of the rolandic fissure.

Kennard (Age and Other Factors in Motor Recovery from Precentral Lesions in Monkeys, *Am. J. Physiol.* **115**:138-146, 1936; Recovery of Function in Infant Monkeys Following Cortical Ablations, *ibid.* **123**:118, 1938; Reorganization of Motor Function in the Cerebral Cortex of Monkeys Deprived of Motor and Premotor Areas in Infancy, *J. Neurophysiol.* **1**:477-496, 1938; The Relation of Age to Motor Impairment in Man and Subhuman Primates, ARCH. NEUROL. & PSYCHIAT. **44**:377-397 [Aug.] 1940) reported that decortication of infant monkeys produced paresis of the contralateral arm early in infancy and that as development proceeded spasticity appeared.

A search through the records of the Muscle Training Clinic of the Children's Hospital disclosed 7 instances in which a physician had made a diagnosis of brachial palsy early in infancy, only to have spastic hemiplegia supervene. Seven additional examples were encountered in which good descriptions of early flaccid paresis were given by district nurses or parents who brought babies to the hospital for treatment of hemiplegia. Finally, the case of an infant seen in consultation on the seventh day of life because of "brachial palsy" and signs of increasing intracranial pressure is included in the present discussion, since surgical procedures demonstrated the pathologic lesions present in the head. Thus, 15 cases were found in which cerebral palsy, usually hemiplegic, was confused early in life with a peripheral injury.

Of the 15 babies, only 5 had normal natal or neonatal histories. The mothers of 2 had pneumonia at the time of delivery; 5 were delivered by forceps, and of these 1 had a right occipitoparietal hemantoma of the scalp and subsequent left hemiplegia. One was delivered by breech extraction; 2 others had hemorrhagic disease of the newborn sufficiently severe to require transfusion, and 1 nearly died of exsanguination when the umbilical cord became untied. There were, therefore, an unusually large number of babies with abnormal birth histories.

Of the 5 remaining infants, paresis developed in 1 in the course of syphilitic meningitis, and no etiologic factor could be discovered for the remaining 4 patients.

Anatomic evidence is meager. Encephalographic examination made of the first patient at the age of 15 years showed widespread atrophy of the involved hemisphere and shift of the intracranial contents toward the affected side, findings interpreted as due to a lesion occurring either in fetal life or in very early infancy. The last patient had bilateral subdural collections of fluid, that on the side opposite the affected area being encapsulated. The eleventh patient had acute syphilitic meningitis.

The most striking thing about the clinical course was that the weakness of the arm in the patients whose lesions were presumably natal or neonatal was noted on the day of birth in only 2 instances. In all the other infants it appeared a few days, weeks or months after birth.

In most instances the paretic arm was described as "weak" or "not used as much as the normal one." The word "motionless" was used by the parent or physician in only 3 cases. The reflexes were inconstant. The range of passive movement at the wrist and finger joints was increased in 1 case.

In most infants the hemiplegic nature of the paresis was noted when they began to walk, but in 6 infants paresis of the affected leg was noted between 7 days and 1 year of age. It was never complete, and active movement was more or less preserved. In 1 infant passive movement at the ankle joint was increased in range.

The age at which spasticity supervened is difficult to determine. In 1 child tetraplegia developed, which has continued to show mixed spasticity and flaccidity, and 4 other infants were not observed sufficiently frequently. The remaining 10 showed spasticity between the ages of 7 months and 2½ years.

The series contains an unusually large proportion of infants showing paresis of the face, a finding interpreted as indicating widespread cortical involvement. Kennard has shown that in infants with cortical lesions innervation of the face is probably undertaken by other than the usual cortical areas unless the cortical lesion is widespread. Her work also demonstrated that no motor disability appeared early in infant animals unless widespread cortical ablations were made. In the present series, with 1 exception, all the infants who showed weakness of the arm within the first month of life showed facial involvement after the adult hemiplegic pattern was established. These facts suggest that only widespread cortical lesions produce motor disturbances in early infancy in man.

The evolution of infantile hemiplegias has been described. In early infancy weakness and hypotonia are the outstanding signs. They tend to be most marked at an interval of days, weeks or months after birth, are more obvious in the hand and arm than in the leg and foot and are least pronounced in the musculature of the trunk. With mild involvement these signs take the form of disinclination on the part of the infant to use the extremities. It seems likely that the mild early symptoms of this syndrome easily escape attention, but it is also probable that relatively circumscribed lesions of the cortex in the newborn produce no observable changes.

In the latter half of infancy paresis becomes replaced by spasticity, or spasticity appears without previous overt involvement, with all the well recognized neurologic signs and symptoms of cerebral motor disturbance.

The sequence of weakness and hypotonia followed by spasticity occurs as the result of damage to the infantile cortex. Gradual processes of maturation going on in the brain as a whole are probably responsible for the progressive changes which continue long after myelin has begun to appear in all the tracts which become myelinated in the adult.

It is hoped that closer observation of young infants may disclose more cases of hemiplegia in the early stages and lead to a better understanding of the acute pathologic changes involved.

DISCUSSION

DR. BENJAMIN BURLEY, Worcester, Mass.: How frequently does one see a subdural hematoma in an infant under 1 year of age? The present case reminds me of a child I saw six years ago. The child, then 6 months old, had been referred as having hydrocephalus. After investigation I found that the infant had had a slight fall about one month before. I made a puncture through the fontanel and removed over a pint (475 cc.) of bloody serum; there was the diagnosis! The child made an excellent recovery.

DR. ALEXANDRA ADLER: Are the chances of recovery better when only the cortex is injured?

DR. WILLIAM G. LENNOX: How many of these children have seizures? What is the differentiation between an injury of the brachial plexus and a cortical lesion?

DR. H. HOUSTON MERRITT: What is the earliest age at which Dr. Byers has seen choreoathetosis develop?

DR. WALTER WEGNER: Dr. Byers mentioned that in 1 case the child apparently had an injury of the brachial plexus at first. Could one differentiate on the basis of the presence or absence of the reflexes?

DR. RANDOLPH K. BYERS: The frequency of subdural hematomas depends on the definition. Whether one considers them to be common, less common or rare depends on whether the diagnosis is made in all cases in which subdural fluid, varying from pure blood to clear fluid, is obtained. To classify the condition as a subdural hematoma in a case in which the latter is present seems open to argument. In my opinion, clear subdural fluid probably accumulates to fill a deficit rather than as a result of injury.

As to the age at which choreoathetosis appears, I have only a vague impression, although I have never made the diagnosis in a child less than 2 or 2½ years of age.

As to the presence of fits in the acute stage of the injury: The little boy with hemiplegia in whom nothing was found had generalized twitchings. The first patient had fits when 14 or 15 years old, and the baby whose hematoma was removed, now recovered, had fits when about 12 days old, just before operation. Others had occasional seizures.

The differential diagnosis of injury of the brachial plexus and cortical injury is difficult. The reflexes are not a reliable guide. It is difficult to obtain arm jerks in a baby. One certainly cannot get reflexes in the flaccid arm of the child with hemiplegia or in the arm of a baby with brachial palsy. There is a difference in the way the baby looks. In an infant with hemiplegia the arm is usually relatively motionless, but if he is stirred up he can usually move it. In the case of injury to peripheral nerves paresis is at a maximum at the moment of delivery (provided it took place then) and tends to improve. Involvement of the homolateral leg is not necessarily a means of differentiation, since this condition may be present in patients with peripheral lesions affecting the arm (brachial palsy) if the spinal cord is also injured. Involvement of the spinal cord through the spread of hemorrhage or edema up nerve roots may cause paralysis of the leg in connection with brachial palsy.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

LINUS J. FOSTER, M.D., *President, in the Chair*

Regular Meeting, Nov. 14, 1940

Cerebellar Abscesses of Otitic Origin in Nine Children. DR. FREDERIC SCHREIBER, Detroit.

Nine children with cerebellar abscesses following mastoiditis were operated on, with complete recovery in 8 cases. The average age of the children was 6 years, and the diagnosis of abscess was made within two or three weeks after mastoidectomy. Although the children were stuporous, ataxia and atonia of the arm on the same side as the abscess could be demonstrated in each case. Headache and vomiting were present in all cases and choking of the optic disk in most.

In each case operation was delayed as long as possible without jeopardizing life from increased intracranial pressure. Introduction of any additional anoxic factors was avoided. Morphine or other sedatives were not given. Sulfanilamide was discontinued as soon as a diagnosis of abscess could be made. Lumbar puncture was also avoided when a cerebellar abscess was suspected.

Local anesthesia only was used in each instance. Through a 1 inch (2.5 cm.) incision a small burr opening was made at a point halfway between the occipital protuberance and the mastoid tip. The dura was incised enough to permit the introduction of a small blunt cannula. Resistance of the wall of the abscess was usually met at a depth of 2 to 3 cm., and 20 to 30 cc. of pus flowed from the cannula. When no more pus could be obtained, the cannula was withdrawn and the wound tightly closed with silk. Culture yielded Streptococcus haemolyticus in 7 cases and Staphylococcus in 2 cases.

In the cases of 2 children a secondary aspiration was necessary. One child who died the third day after operation had preoperative "cerebellar fits" after lumbar puncture, and proper waiting for walling off was not possible because of the poor condition of the patient. The 8 surviving children have been observed for periods ranging from eight years to eight months and show no demonstrable sequelae.

DISCUSSION

DR. ALBERT S. CRAWFORD, Detroit: Dr. Schreiber's unusually favorable results for cerebellar abscess call for a careful evaluation of the various factors involved in the diagnosis and surgical treatment of abscess of the brain.

The fact that most of his patients recovered is evidence that the abscesses were well walled off and that the patients had already acquired a safe degree of immunity to the infection. It cannot be too often emphasized that sufficient time must be given for complete walling off of the infection.

It is commonly known that it requires from three to six weeks for the formation of a good abscess wall. The chief clinical signs that indicate the degree of walling off are subsidence of the signs of meningitis, lessening of the cell count in the cerebrospinal fluid to nearly normal and a steady increase in the number of lymphocytes to nearly 100 per cent.

Dr. Schreiber has stated that he did not operate until the abscesses seemed to be well walled off. It does no good to operate before this has occurred, for the results of surgical intervention then are usually tragic. It is difficult for the neurosurgeon to delay the time of operation long enough if the physician in charge of the case is constantly pressing because the patient does not seem to be doing well. The decision as to when to operate is often the most difficult a surgeon has to make and to persist in a conservative course calls for a great deal of courage, for sometimes the abscess will rupture, usually with fatal results, while one is waiting for the proper time to operate.

A part of the problem which particularly interests me is that of natural immunity. Why is it that in some cases good abscess walls form and in others not? I wonder if Dr. Schreiber has, or could obtain, data on these patients who survived as to their natural resistance to infection in general, their lack of tendency to "catch colds" or their freedom from allergic sensitivity. I have a feeling that this factor may be important. Is it possible that artificial immunity might be built up in those who seem to lack such natural resistance and thus perhaps the development of meningitis or encephalitis be prevented in the future? Does a person who lives a more sheltered life, under more hygienic conditions perhaps, thereby lose out in the development of natural immunity? A careful study of the cases of patients who survive infection and of future cases as compared with those in which the patients die of their disease might prove of value in efforts to solve this baffling problem.

Time does not permit fuller discussion on such points as the surgical technic employed, the subsequent aspirations which are necessary or the proper procedure in cases in which there is impending death when the abscess is not properly walled off.

DR. MAX T. SCHNITKER, Toledo, Ohio: I should like to ask Dr. Schreiber about his technic in treating cerebellar abscesses. Did he carry out the technic of a single aspiration of the abscess with a puncture needle, as advocated by Dandy and Vincent, or did he insert an indwelling cannula for continuous drainage? If the latter procedure was used how long was the cannula left in place?

DR. EMIL AMBERG, Detroit: My case, of which Dr. Schreiber spoke, concerned a child 4 years old with a cortical cerebellar abscess. The child recovered (*J. Michigan M. Soc.* **6**:99-105, 1907). It is claimed that a capsule forms in eighteen to sixty days. Sometimes there is no capsule formation, when anaerobic or certain other micro-organisms are present (Neumann). Multiple abscesses may complicate the situation. Great care must be exercised in the use of the new drug in treatment of mastoiditis. Besides masking the symptoms, the drug may be dangerous in itself under certain conditions.

DR. E. S. GURDJIAN, Detroit: Whether an abscess of the brain is treated by a single tapping, by inlying drainage, by decompression followed by evulsion or by uncapping the abscess and removing its contents by electrocautery, the primary consideration from a neurosurgical standpoint has been the appropriate walling off of the cavity of the abscess before intervention. In Dr. Schreiber's amazing series of cases, part of the success was undoubtedly due to waiting long enough for proper walling off to be effected.

In the diagnosis of abscess of the brain, it must also be remembered that the spinal fluid may show a lymphocyte count of 50 to 250 per cubic millimeter, with hardly any polymorphonuclear cells. Such a picture should not discourage the diagnosis of abscess of the brain.

Psychoanalytic Therapy. DR. RICHARD STERBA, Detroit.

A neurotic symptom is caused by the return of repressed instinctual material. The unconscious material returns in a form which has to be disguised on account of the ego's forces of defense, to which the term anticathexis is given. This process is demonstrated by the case of a 22 year old man who became impotent after contracting scabies followed by lymphangitis as a result of intercourse. At this time there developed the neurotic sensation that his hair was standing on end. The symptom was traced back to childhood experiences. An explanation is given of how the determinants of the symptom were discovered through analysis. During this procedure obedience to the fundamental rule brings about an enlargement of consciousness over memory traces hitherto inaccessible. The fundamental rule leads to relaxation of the ego defenses, whereon infantile object relationships are repeated with the analyst, which phenomenon is termed transference. The transference is the most important means one has of recognizing the repressed emotional experiences of early childhood.

DR. LEO H. BARTEMEIER, Detroit: The fundamental principle in psychoanalytic therapy consists in bringing about changes in the structure of the neurotic personality through changing the interplay of the basic forces in the psychic life and therefore the conflicts which lie behind the neurosis. In the neurotic personality one finds quantitative disharmonies between the ego and the id, and, as Dr. Sterba has clearly pointed out, the object of the therapeutic task is to establish a better quantitative balance between these psychic provinces. Not only is the psychoanalytic therapy a procedure during which the patient gains a better intellectual understanding of himself, but, more important, it is a profound emotional experience during which he reenacts and relives many of his earlier experiences. These are repeated in connection with the analyst, who, in the role of a surrogate parent, attempts to correct the mistakes which were made by the original educators.

DR. J. CLARK MOLONEY, Detroit: There is one point in Dr. Sterba's paper which I feel should be constantly emphasized. I refer to his comments about resistance. Because of the ego's resistance to unconscious instinctual demands, the ego is capable of many mechanisms of defense. One of these mechanisms, which is interesting and extremely important, is the capacity of the ego for withdrawing attention from any problem or subject which may bring to attention painful situations or realizations. I do not doubt that this mechanism has been put into effect by many of those here, even as Dr. Sterba talked. This, assuredly, would lead to many blindspots. This withdrawal of attention on the part of the ego, a manifestation of resistance, constitutes one of the most important reasons that it is so difficult to explain psychoanalytic mechanisms through the medium of a lecture.

Resistance, and the mechanism of withdrawal of attention from painful realizations, may be known to many in a more or less superficial, intellectual way. However, one does not gain a real emotional comprehension of the intensity of resistance, and of ego defenses, unless one has undergone analysis, or unless one is doing therapy in a psychoanalytic sense. It is in this situation that one becomes aware of the true emotional meaning of resistance.

DR. LOUIS A. SCHWARTZ, Detroit: It was unfortunate that Freud postulated his theories at a period in the development of medicine when it was just emerging from the dark ages of mysticism into the period of "laboratory scientific" method. It was therefore with reluctance that the medical profession considered Freud's point of view, as it seemed to them to be too reminiscent of the period of medicine just passed. Also, the resistance of people in general to accept the fact of infantile sexuality limited still further the development of psychoanalysis. The psychoanalytic movement itself has passed through three more or less definable epochs—the first being concerned with the primitive, instinctual forces, the second with the emphasis on repression and the results of "conscience" and the third with the emphasis, during the last two decades, on the understanding of the defenses of the ego and the adaptation to reality of the organism. This change in emphasis has also drawn attention to the interrelationship between soma and psyche and to the relationship between physiologic disturbances within the vegetative nervous system as a result of emotional conflict. This point of view has, in fact, given rise to what may be termed "psychosomatic medicine." Psychoanalysis has shown clearly that many of these disturbances seen in the adult have their origin in the early experiences of childhood, namely, in the infantile neuroses.

DR. IRA ALTSHULER, Detroit: I do not rise to attack the principles of psychoanalysis as a philosophy or a doctrine. It would be presumptous indeed on my part to attempt to minimize the immortal works of Freud. What puzzles me is some of the impracticabilities of psychoanalytic technic. Dr. Sterba has just mentioned that the psychoanalyst must be a therapeutist and a research worker at the same time. Now this, to me, is a great practical handicap. Many good psychiatrists may be poor research workers and vice versa. It is usually the personality of the psychiatrist and his rapid and successful rapport with the patient which count more than his ability to built a research scheme during therapy. Research work is slow, needs checking and rechecking and is thus quite impracticable in the treatment of neurotic patients, who should get the benefit of *"cite, tute, et jucunde."* What, then, does Dr. Sterba mean by research when orthodox psychoanalysis a priori delineates the sphere in which the analyst may operate, that is, within the concepts of the id, ego and superego, transference, and the like? Is there, under such circumstances, any room left for further independent expansion for the therapeutist? The economic factor in the practice of psychoanalysis is the crucial point in the situation. Are the psychoanalysts determined to treat only the wealthy patients? The money and time required for psychoanalysis is beyond the pocketbooks of too many patients. I have not heard of psychoanalysts disbursing charity to the same degree as does the general medical man. There are other practical shortcomings one can point out, but these may be left for some other time.

DR. MILTON H. ERICKSON, Eloise, Mich.: I should like particularly to stress the importance of adequate recognition and understanding of emotional reactions, since these really cannot be verbalized however articulate the patient may be, and since the actual therapeutic outcome of the analytic process depends so extensively on the experiencing of emotional reactions rather than merely on verbalizing free associations.

There is one question, however, I wish to raise for general consideration. This question relates to the present emphasis placed by the analytic procedure on the need for the patient to become consciously aware of his thoughts and feelings, his memories and fantasies—in brief, the emphasis placed on as extensive as possible a conscious awareness of his experiential past. Yet it is self evident that, no matter how long continued the analysis may be, there really can be no complete conscious review of everything, and that hence there must necessarily be much dependence on unconscious processes and insights. So, despite the emphasis on conscious awareness at the present, I wonder whether future psychoanalytic research will not deal more and more with the problems of unconscious processes and insights.

Book Reviews

The Organism. By Kurt Goldstein, M.D. American Psychology Series, Henry E. Garrett, General Editor. Price, $4. Pp. 553. New York: American Book Company, 1939.

The significance of this book by Dr. Kurt Goldstein is given in two passages, one in the preface to the German edition, the other in the introduction. "The intention to write this book goes back many years. It dates to that time of the World War when it became my special task as a physician to take under my medical care a great many patients with lesions of the brain." "Hitherto, the aim of biological research has been to divide the organism, like any physical object, into parts, and then to reconstruct it. But this procedure has yielded few satisfactory results either in respect to the physical or the psychic phenomena of an organism. Dissatisfaction with these results has been one of my motives in restating the problem . . . The basic motive, however, was not primarily a dissatisfaction with the theoretical results, but with their *inadequacy in medical practice.*" "The Organism" is a combined protest and plea: a protest against the classic neurologist, a functional anatomist who would rather see an autopsy to check his diagnosis of localization than expend a different type of effort to deal with the patient as a suffering human being; a plea for a constructive theory to correlate the various biologic sciences with the central problem of dealing with patients. The author's strong convictions in these regards have led him at times to formulations and generalizations which will be considered by many to be extreme, or even incorrect. His work, however, will remain a monument to a fundamental point of view which has already widely permeated biologic thinking and which must eventually become part and parcel of all attempts to formulate behavior in any of its aspects.

A considerable portion of the book is devoted to a critique of the various concepts and theories purporting to describe organismic behavior. In general the criticism is not directed at the technical method or at the data, but at the attitude of such observers as those who maintain that the behavior of the whole organism can be adequately described by generalizations derived from observation on artificially isolated parts of the organism. Much of Dr. Goldstein's criticism of the anatomic, physiologic and biochemical approaches to the study of the nervous system seems at present to be in the nature of setting up a straw man in order to knock him down. However, it may be justly claimed that the point of view Dr. Goldstein champions cannot be overemphasized. Some of his criticism unfortunately loses force, owing to the fact that he has not taken into account much of the more recent data. This applies particularly to his discussion of variability of reflexes and of specificity in the autonomic nervous system. Certain of his comments, however, are arresting and warrant further attention. Thus, he points out that the concept of inhibition in the central nervous system is merely an auxiliary hypothesis, used to account for absence of activity in response to stimulation, and that the phenomena concerned may be formulated without assuming any such qualitatively different process. Dr. Goldstein also maintains that phenomena such as reflex reversal and reciprocal innervation are produced by the technic of the experiment. In the intact animal one is in reality dealing with different whole performances, in the first case, and with a single whole performance, in the second case. Another important concept advanced is that reflexes (that is, rigidly set responses to definite stimuli) occur rarely in intact organisms. The simpler the organism, the more completely is it embedded in its environment and the more its behavior is that of total performances. Such total performances show great variation, depending on the nature of the organism.

Reflexes rigidly defined can occur only in isolated parts of the organism. It is likely that under normal conditions it is only the proprioceptive reflexes which occur, and these only in the more complex organisms which are relatively independent of their environment, and so come more frequently into emergency or "border" situations.

The subject of conditioned reflexes receives less consideration than would seem to be deserved in a book of this kind. Conditioned reflexes are rather summarily dismissed as of no value for understanding normal organismic behavior for two main reasons. First, on the basis of a number of categorical statements regarding their formation, instability, rigidity, and the like (to which exception may justifiably be taken), they are said to be alien to the organism and to be of the same nature as other reactions taking place in artificially isolated parts. Second, they are characterized as "drill results"—"drill" meaning "every sort of so-called training, without primary insight"—and they are said probably not to occur under natural environmental conditions. Dr. Goldstein, however, points out that "there is probably an essential difference between animals and man, in this respect." Probably only man is capable of self adaptation to the unaccustomed, unnatural situation required for achieving "drill results." When insight is gained, however, reactions learned in this way become total performances of, and with meaning for, the whole organism. In discussing "instincts" and "instinctive behavior" Dr. Goldstein rejects the explanation that they are "chain reflexes" and also the concept that they are fundamental patterns out of which the rest of behavior is constructed. He regards instincts as performances of the whole organism in no way different from other performances, except that inborn and nonconscious motives play an important role. In many cases they appear at a certain stage of maturation and are later displaced by the higher, volitional type of performance.

With regard to the "so-called drives" Dr. Goldstein is a monist. "Only one drive: self-actualization. Normal behavior corresponds to a continual change of tension, of such a kind that over and again that state of tension is reached which enables and impels the organism to actualize itself in further activities, according to its nature." Any theory of multiple drives has to assume some "higher agency" to decide between them. The postulation of a number of separate drives has been due to the fact that observations have been made chiefly on persons who were ill or on normal subjects under extreme emergency conditions. With a single drive the organism actualizes those potentialities which are most important for it. Deviation from this rule Dr. Goldstein regards as "abnormal." Further phenomena, such as obsessions, compulsions and rituals, are considered to be habits and mechanisms which have lost their meaning for the organism and so have become autonomous.

There is a rather extensive discussion of localization and specificity in which the older, more rigid views are refuted. Dr. Goldstein finally concludes that there is a "special significance of specific structure." "This does not imply that that quality, which the functioning of any part contributes to the organism's performance, exists *by itself* outside of that whole relation." "The specificity itself arises within the functional pattern of the whole to which each part, by functioning, contributes a very specific qualitative tonality."

Dr. Goldstein criticizes freudian psychology on three main bases. First, he objects to the rigid, static, almost structural nature of the concept of unconscious and conscious. Dr. Goldstein prefers a more dynamic, biologic approach. He regards those phenomena which are included in the term unconscious as the reappearance in the adult of early, immature ways of coming to terms with the environment. He points out that these phenomena are frequently endowed, either by the patient or by the observer, with content and meaning which they certainly did not have at that stage of development when they appeared first, and when they were the normal form of behavior. He objects to the idea that former reactions and attitudes are actively repressed. Instead he feels that with

maturation new attitudes and reactions are developed, of which the former reactions are no longer a part and so become obsolete and discarded. Second, Dr. Goldstein rejects the theory that personality difficulties are due entirely to abnormalities in the development of the sex life of the individual. He regards the symptoms in the sphere of sex as merely one of the symptoms of the illness of the whole personality. Finally, Dr. Goldstein criticizes caustically Freud's concepts of the pleasure principle and of the death instinct. "Life in the so-called unconscious appears, in Freud's conception, as dominated by drives, dominated in such a way that it becomes the life problem to obtain relief from the tension the drives create. This release, according to Freud, represents the goal of all drives, especially of the sex drive. The goal of the sex drive is the 'becoming free' of the tension of sex—that is the essence of the pleasure principle." "This view of Freud, that life is dominated by a drive, the nature of which is to lead to release, must necessarily carry us to the further view which Freud, with his characteristic consistency, has finally advanced, namely, that the *ultimate goal is the complete release, or death*—the disintegration into the inorganic. When Freud realized that his concept of a libidinal drive does not cover all aspects of human behavior, he introduced the death instinct." Dr. Goldstein goes on to point out that such a negative theory fails to do justice to the positive aspects of life. Thus it "does not do justice even to the biological value of sex, to its positive significance for the actualization of the nature of the human being, to the real significance of what he calls the unconscious." It naturally follows that such a negative instinct theory fails to account for all those phenomena included in the term culture.

Practically an entire chapter, chapter 8, is devoted to a discussion of gestalt psychology and the theory of the physical *Gestalten*. Dr. Goldstein points out that although gestalt psychology comes closer to his point of view than do other systems, yet there are two fundamental differences. First, gestalt psychologists have dealt mainly with isolated phenomena, that is, with performances in limited fields (e. g., the visual perceptive field, the auditory perceptive field, the sensory motor field), whereas Dr. Goldstien is interested in the total performance of the whole organism, in the "nature" and "meaning" of the whole organism. Second, the theory of physical *Gestalten* assumes return, following a stimulus, to a dynamic equilibrium, whereas for Dr. Goldstein the return is to a state of adequate tension. Also, "the claim of isomorphic and invariably 'non-arbitrary' Gestalt patterns does not leave sufficient room for a positive determination and explanation of a phenomenon which is, in particular, an attribute of the human being." This attribute is the ability for voluntary shifting, for reasoning discursively, for free decision for action, and the like.

The positive contributions in the book may be considered under three headings: a summary of Dr. Goldstein's important observations on patients with lesions of the forebrain and cerebellum; a discussion of the holistic point of view, and a description of the function of the nervous system. It should be pointed out that Dr. Goldstein's concepts are based on his technic of investigation. This technic consists essentially of gross observation of the overt behavior of the subject. Dr. Goldstein recognizes fully that the overt behavior is modified, or may even be determined, by such factors as the type of "personality" of the subject, the subject's temporary attitudes, feelings, moods and affects and the peculiar significance of certain situations for the subject. He deals with these factors, however, only in blanket terms. In other words, Dr. Goldstein's technic excludes direct investigation of those data which belong, par excellence, to the field of psychiatry. The contributions of the book which most closely approach psychiatric problems are the discussions of the unconscious (referred to previously) and of anxiety. Dr. Goldstein is one of the first investigators to recognize that in the processes of learning and of adapting to new situations anxiety is normally present. He does not regard anxiety as a stimulus to accomplishment, but rather it is a "catastrophic reaction" which requires "courage" to be tolerated or overcome. In this

opinion Dr. Goldstein recognizes quantitative, but not qualitative, differences between minor states of anxiety and such excessive states as may possibly better be termed "panic."

In the first chapter Dr. Goldstein outlines the manner of the disintegration of function following cortical lesions and summarizes a set of "rules determining organismic life" on the basis of his observations of patients. The reader is referred to the original publications for most of the data, only the briefest, general descriptions of symptoms being given here. Throughout the book illustrative material from Dr. Goldstein's observations are used in conjunction with the theoretic discussion, and a few brief case histories are given. A number of important comments on dealing with patients are made, and the nature of the physician-patient relationship is discussed practically and constructively. In my opinion, the book would be much more valuable if Dr. Goldstein's observations on patients had been given systematically and in some detail, even if the inclusion of this material had necessitated reduction of the theoretic discussion, with which the greater part of the book is concerned.

Dr. Goldstein's discussion of the holistic point of view is necessarily essentially metaphysical—in the sense that he is dealing with principles rather than with facts—except when he is criticizing rigidly defined theories. It is inevitable that the holistic view is developed in the book as a criticism of a theory of this nature, namely, the outmoded theory of rigid reflexology. The reason for this is that, from the holistic point of view, one must know the "whole of the organism," its "essence," its "true nature," on the basis of which it is alone possible to understand its behavior. But how does one arrive at such knowledge? As Dr. Goldstein points out, only by studying artificially isolated parts of the organism, by discriminatory and differentiating investigation. From such part pictures a sketch of the whole is made. Later, discrepancies are found, further observations made and a new approximation of the true nature arrived at, and so on. Thus productive data come from experiments on parts, and the concept of "the organism as a whole," or the concepts of the "prototype (in the sense of Goethe's *Urpflanze*) of the individual," "the prototype of the species" and the "prototype of nature" are necessary for criticism of theories and speculations based on the data. In other words, one must recognize the limitations of scientific technic and always remember that: "There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy," and that the organism does what it does because it is the organism and not because of the rule of thumb one thinks one has worked out for it.

Dr. Goldstein attempts to describe the function of the nervous system on the basis of gross observation of behavior, using a terminology which avoids any commitment to any concept of mechanism. Such a point of view and terminology not only preclude discussion of mechanism, but also preclude discrimination on the basis of external criteria, as well as any quantitative measurements. The nervous system is a "network." After a stimulus there is "spread of excitation," followed by an "equalization process," with return to a state of "adequate tension." There are "near" and "distant" effects, resulting in the "figure-ground" formation. If the response of the organism is "adequate" the behavior is "preferred" or "ordered" behavior. Otherwise the organism suffers a "catastrophic reaction." Dr. Goldstein does not analyze the catastrophic reactions. The immediate effects of cerebral trauma, anxiety and in certain instances of sleep are thus characterized, however. Activities of the organism may be "equalization phenomena," "turning-to" reactions, "defense" reactions, "flight" reactions, "adjustmental" shifts, "instinct" performances or "volitional" performances. The confusion that arises is well shown by the discussion of the Babinski phenomenon in conjuction with the discussion of flexor and extensor movements. The Babinski phenomenon is a flexor movement executed by extensor muscles. It is not, however, a "flexor performance," nor is it a "turning-to reaction," both of which are also usually, though not always, flexor movements, whether achieved by flexor or by extensor muscles.

Instead, the "Babinski phenomenon is a rudiment of a flight reaction." No objective criteria for differentiation between these various categories of response are given, but by inference from the general discussion it seems that the conclusion must be reached on the basis of the observer's personal impression as to the objective of the response.

In conclusion, the main features of "The Organism" may be summarized as follows: Impelled by the desire for a humane treatment of patients with chronic neurologic disease, Dr. Goldstein has written a vigorous, constructive, positive presentation of the thesis that to understand truly a living being it is necessary to comprehend "the whole of the organism." In developing this thesis Dr. Goldstein incisively criticizes certain theories of organismic behavior which are founded on experiments on isolated parts of the organism. He also raises many points richly deserving attention and further investigation. He has made one of the few attempts in the literature to develop a single set of concepts and a uniform terminology to cover all the aspects of organismic life. However, all such attempts are at present doomed to failure on theoretic as well as practical grounds, owing to the inextricable manner in which the observer, the technic of investigation, the concepts and the terminology are bound together. As a clinical neurologist, Dr. Goldstein's technic has consisted in large measure of observation of the overt behavior of the subjects (mostly patients who have survived injury to the nervous system). His concepts and terminology represent thus a broad biologic view of clinical neurology and behavioristic psychology. The data comprised in the fields of psychiatry, biochemistry, cytology and electrophysiology, for instance, are admitted, but not integrated. The present wide variety of technics inevitably leads to different concepts, and it remains for the investigator in any one field to bear in mind Dr. Goldstein's main thesis.

The Neuroses in War. By E. Miller, Editor. Price, $2.50. Pp. 238. New York: The Macmillan Company, 1940.

This valuable treatise should be required reading for medical officers of the armed forces. It might also serve as a manual of practical, informal psychotherapy for civilian practitioners. It is a collection of well coordinated essays on the psychologic problems encountered in military medicine and in countries at war. There has evidently been a close collaboration between the various authors, so that duplication is at a minimum. The fact that it has been written by many hands is a considerable safeguard against any suspicion that facts were being selected to justify the prejudices of an individual.

The spirit of the book may be illustrated by the following passages from the preface:

"But let us not dismiss the man who breaks down with neurosis in wartime. As a group, the psychological patients of the last war served as long and at least as well as the average soldier. There is official evidence to show that in a very large proportion of cases, before the breakdown, the man has done credit to himself and his unit. Against overwhelming mental forces calling him to abandon his struggle to fight on, he has frequently carried on. In fact the proportion of men with neuroses who received decorations for valour showed little difference from the proportion of other soldiers who received decorations. It would appear that some measure of mental peculiarity may endow a man with élan, with conscientiousness and sometimes with additional grit.

"Furthermore, the civil population are no longer outside the war. A. R. P. has provided them with some measure of physical protection. But they must be protected also from their own mental reactions. Being less organized than mobilized men and women, they have not the protective armour of discipline and the immediate loyalty which membership of a unit engenders, which would do much to safeguard them from feelings of insecurity. These millions must be catered for in the 'War of Nerves' and in the war which may encroach upon the home front. Doctors, therefore, in civil life, in the A. R. P. units, and the Emergency

Medical Service, need to know something about the neurotic sequelae of an air raid and the ways in which a slowly developing war with an almost elephantine period of gestation impairs the morale of a community."

A particularly interesting chapter is that on the mode of onset of war neuroses, by Dr. Millais Culpin. It is rich in actual verbatim descriptions by patients of the circumstances leading up to their disability, which are most enlightening. In a footnote, the author remarks:

"This method of reviving memories was regarded as an application of psychoanalysis—at that time under general condemnation. Any attempt at discussion of the method was likely to be met by charges of obscenity. It was denied that memories were suppressed; that, if suppressed, they could be restored; and that, if restored, they had any relation to the symptoms. Those who used the method were supposed to be peculiarly credulous people fooled by artful neurotics or malingerers. A study of the contemporary literature will give general confirmation of those statements. An immediate result of this curious situation was that, although there was ample material for testing out the new ideas, that material was wasted. As a secondary result the work found no record in orthodox literature and it is now possible to read, in standard textbooks, chapters on the psychoneuroses of war written as if this way of approach had never existed. Some elements in the present situation cannot be understood without a knowledge of this fragment of medical history."

While the point of view of most of the contributors is decidedly hospitable to the conception of unconscious motivation and the role of long-past experience and of personality types in the production of acute neuroses, the approach is nowhere sufficiently psychoanalytic to bring a blush to the cheek of any physician. Sexual problems are mentioned only in passing. There is a notable absence of technical psychologic terms.

The review of literature is excellent. The work of the neuropsychiatrists of the United States Army during the last war is praised. It is evident that they did not neglect the opportunity to learn from the experience of the earlier combatants.

Principles of Psychiatric Nursing. By Madelene Elliott Ingram, R.N. Price, $2.75. Pp. 428, including glossary and index. Philadelphia: W. B. Saunders Company, 1939.

This book presents in clear, concise and readable manner the practical aspects of psychiatric nursing. The material is conveniently arranged in four units. Unit 1 summarizes the historical background of the care of the mentally ill. Unit 2 is a comprehensive presentation of factual material on nursing care related to specific situations and conditions. Unit 3 introduces the student to some of the significant factors of behavior, with methods of observation and recording, and to the purposes, technic and administration of some of the specific psychiatric treatments. Unit 4 deals with extramural problems and concludes with principles of mental hygiene. Throughout the book are summary outlines, questions and references, which enhance the usefulness of the book to both teacher and student.

Bacteriology in Neuropsychiatry: A Survey of Investigations Concerned with the Specific Role of Infectious and Immune Processes. Nicholas Kopeloff. Price $4.50. Pp. 294, + index. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

According to the preface, "The purpose of this book is to present succinctly the contributions which bacteriology and immunology have made to the study of nervous and mental disorders. . . . In general, there is a marked contrast between the contributions made by bacteriology and immunology to the *etiology of somatic disease* on the one hand, and to *psychiatric disorders* on the other."

The most valuable features of the book are the bibliography and the review of the part which infections and intoxications has been alleged to play in the major psychoses.

Chapter 1, on the diseases of known origin with primary involvement of the nervous system, includes syphilis (for some obscure reason), epidemic meningitis, the infectious encephalitides, herpes, rabies and poliomyelitis, in 50 pages. Chapter 2, diseases of known origin with secondary involvement of the nervous system, includes abscess of the brain, tuberculosis, leprosy, the rickettsial diseases, some spirochetal diseases, the virus diseases, protozoal diseases, infestation with worms, the diseases in which toxins involve the nervous system and a group of coccic and bacillary diseases, all in 121 pages. The description of each disease is usually shorter than that allotted to it in textbooks of medicine.

Under the heading "Diseases of Unknown Etiology Involving the Central Nervous System" (chapter 3), most of the space is devoted to a discussion of the various theories—by now numerous—which attempt to explain the "functional" group of psychoses as due to infection or intoxication. The review is extremely critical and on the whole well done. Epilepsy is included in the group.

The author expresses the belief that lethargic encephalitis is due to a virus but points out the unsatisfactory nature of the evidence. He groups multiple sclerosis and migraine as noninfectious diseases and takes on the whole a skeptical position in regard to the allergic origin of the latter.

A brief, fairly adequate review of the immunology of the nervous system is appended. One misses, however, a reference to Finley's work on the "allergic" nature of the postinfectious encephalitides and any mention of "central carotid shock."

On the whole, this book is uneven in value. The discussion of the clinical features of the acute exanthems and other familiar diseases might well be spared and corresponding space be devoted to the author's own valuable work. Collaboration with an experienced clinical neurologist and neuropathologist might also improve the arrangement and emphasis.